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KINETICS OF REACTION OF ALKYL CHLOROFORMATES WITH ALIPHATIC AMINES

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Kinetics of alkyl chloroformates reactions with aliphatic amine series in aqueous and alcoholic media is investigated. Dependence of reaction rate constant on amine structure is described by the modified Taft equation. Reactivity of amines is determined by the inductive effect of H-atoms and by the steric constant of RR'N fragment. The influence of chloroformate structure on acylation rate of 2-aminoethanol is estimated within the framework of the Taft equation. The solvent nature influence in the ROH series (R = H, CH_3, C_2H_5, i-C_3H_7) is investigated for 2-propyl chloroformate reaction with 2-aminoethanol. The process rate is found to be determined by the medium basicity.

Kinetics of alkyl and aryl chloroformates reaction with anilines and fatty aromatic amines has been studied in detail. There has been found correlation relationship between the reaction rate constant, amine and chloroformate structures and medium properties (see work[1]). Simultaneously, the quantitative regularities of reactions of chloroformates with aliphatic amines are poorly investigated. A few works written on this subject[2,3] is not certainly enough and they

do not enable us to efficiently judge the influence of different factors upon the process rate. In this connection it seemed expedient to examine the reagents' structure and the influence of medium properties on the kinetics of alkyl chloroformates with alkylamines as well as to carry out a quantitative interpretation of the obtained result. The latter actually forms the subject of the present work.

$$RR'NH + R''O\text{-}\overset{\overset{O}{\|}}{C}\text{-}Cl \xrightarrow{k} RR'N\text{-}\overset{\overset{O}{\|}}{C}\text{-}OR'' + HCl$$

The kinetics of the reactions was investigated in alcoholic media by the conductometry method, analogous to that described in work[4]. The reaction was conducted in amine, under the pseudo-monomolecular conditions. Independently of the reagent structure the reaction has the second order, the first order is for amine and chloroformate.

The investigation of the influence of amine structure was accomplished on the example of the 2-propyl chloroformate reaction in ethanol. The results are represented in Table 1

Table 1

Rate Constants and Activation Parameters of 2-Propyl Chloroformate Reaction with RR'NH Amines in Ethanol

R	R	T, °C	k, $l \cdot mol^{-1} \cdot s^{-1}$	$\Delta H^{\neq}$, kJ/mol	$-\Delta S^{\neq}$, J/mol·K
1	2	3	4	5	6
H	H	-6.0	0.060 ± 0.001	30 ± 2	154 ± 8
		0.0	0.077 ± 0.001		
		18.5	0.206 ± 0.002		

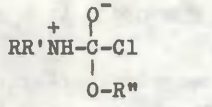
Table 1 continued

1	2	3	4	5	6
CH_3	H	-20.0 -10.0 0.0	5.1 ± 0.3 10.8 ± 0.2 19.3 ± 0.3	36 ± 2	88 ± 7
C_2H_5	H	-15.0 -10.3 -6.0	2.71 ± 0.02 3.96 ± 0.06 5.47 ± 0.08	42.3 ± 0.5	72 ± 2
$n\text{-}C_3H_7$	H	10.0 15.0 20.0 30.0	11.0 ± 0.1 15.2 ± 0.1 19.2 ± 0.1 32.0 ± 0.6	35 ± 1	101 ± 4
$i\text{-}C_3H_7$	H	10.0 20.0 30.0	1.54 ± 0.03 2.84 ± 0.09 4.62 ± 0.11	37 ± 2	111 ± 6
$n\text{-}C_4H_9$	H	15.0 20.0 30.0	15.8 ± 0.3 19.4 ± 0.4 31.2 ± 0.7	31 ± 1	115 ± 5
$s\text{-}C_4H_9$	H	10.0 20.0 28.0	1.88 ± 0.02 3.36 ± 0.02 5.25 ± 0.04	38.1±0.2	105 ± 1
$t\text{-}C_4H_9$	H	20.0 30.0 40.0	0.172 ± 0.001 0.296 ± 0.002 0.436 ± 0.001	34 ± 3	144 ± 9
$CH_2{=}CHCH_2$	H	-10.5 0.0 15.5 25.0	2.29 ± 0.03 4.36 ± 0.03 8.68 ± 0.11 11.4 ± 0.02	28 ± 2	132 ± 6

Table 1 continued

1	2	3	4	5	6
C_2H_5	C_2H_5	11.0 15.0 20.0 30.0	8.82 ± 0.06 10.5 ± 0.1 13.6 ± 0.3 20.2 ± 0.2	29 ± 1	125 ± 3
n-C_3H_7	n-C_3H_7	10.0 20.0 30.0	6.77 ± 0.12 11.4 ± 0.1 16.5 ± 0.3	30 ± 3	122 ± 9
i-C_4H_9	i-C_4H_9	-10.0 -2.0 5.0	1.42 ± 0.07 2.34 ± 0.05 3.58 ± 0.11	35.1±0.3	108 ± 1
cyc-C_6H_{11}	cyc-C_6H_{11}	0.0 10.0 20.0	0.011 ± 0.003 0.018 ± 0.006 0.028 ± 0.006	28 ± 1	179 ± 4
- $(CH_2)_4$ -		-10.0 0.0 14.0	5.46 ± 0.05 14.5 ± 0.7 74 ± 2	22.1±0.5	141 ± 1
- $(CH_2)_6$ -		-20.0 -19.2 -10.0 0.0	16.5 ± 0.6 16.5 ± 0.8 21 ± 1 29 ± 2	14.3±0.9	164 ± 3

The obtained activation parameters are in good agreement with the AE mechanism[1,5] offered for these processes. According to this mechanism, the reaction proceeds via the tetrahedral transition state (1).



(I)

The fact that in general the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values are somewhat higher than those for aromatic amines' reaction[1] can be explained by the differences in the reaction media. Unlike the aprotic dioxan acetone or benzene[1] we investigated the kinetics in ethanol. In this case the amines in solution are in high solvation form (II).

(II)

That calls for the preliminary amine desolvation, which affects the activation parameters. The analogous effect was displayed while alkyl chloroformates' pyridinolysis proceeded in aliphatic alcohols[4].

Table 1 does show that amine structure essentially affects the reaction rate. Its quantitative evaluation is described by the Taft equation[6]. In accordance with the principle of isostericity[7] the steric constants E_s were taken for the RR'N fragment. A number of recent works (e.g, see[8]) prove that the induction effect of the alkyl group is practically identical and it can be taken as being equal to the methyl group, i.e., to zero. In this connection, when examining the influence for the induction effect besides the $\rho^{*} \cdot \Sigma\sigma^{*}$ term , $\rho^{*}_{alk} \cdot \Sigma\sigma^{*}_{alk}$ and $\rho^{*}_{H} \cdot n_{H} \cdot \sigma^{*}_{H}$ were added to the Taft equation; $\Sigma\sigma^{*}_{alk}$ the sum of alkyl substituents' induction constants, n_H - the number of H-atoms at N-atom (1÷3), $\sigma^{*}_{H} = 0.49$ - inductive constant for H atom. The computerized analysis effected for 0° C proved that the effect of the $\Sigma\sigma^{*}$ and $\Sigma\sigma^{*}_{alk}$ pa-

rameters is negligible and the reaction series can be described by equation (1).

$$\log k = 5.597 - (4.433 \pm 0.043)\sigma_H^* \cdot n_H + (1.361 \pm 0.006)E_s$$
$$N = 15;\ R = 0.98;\ SD = 0.042 \qquad (1)$$

Thus, the obtained result testifies to the soundness of the assumption that all inductive constants of alkyl substituents are equal to zero in hydrocarbon series, at least in the case which is considered here. Equation (1) corresponds to the AE mechanism having a kinetically significant nucleophilic attack stage, since the reaction is fairly sensitive to both inductive and steric substituent effects. Besides that the values ρ_H^* and δ agree with the analogous meanings obtained during the analysis of the nucleophilic reactivity of amines with reference to different electrophilic agents[8]. Thus, for instance, for 2,4-dinitrochlorobenzene (ethanol, 25° C) $\rho^* = 4.0$, $\delta = 1.57$; for 4-nitrophenylsulfochloride (benzene, 25° C) $\rho^* = 4.35$, $\delta = 1,56$.

The influence of chloroformates structure on the reaction rate was investigated on the example of 2-aminoethanol acylation in ethanol. Measurement values are given in Table 2.

The activation parameters for ethyl- and 2,2,2-trichloroethylchloroformates do not differ very remarkably. It means that there are invariable mechanisms in the examined reaction series. The analysis of the influence of chloroformate structure within the framework of the Taft equation for 20° C leads to equation (2).

$$\log k = 1.203 + (1.68 \pm 0.06)\sigma^* + (0.806 \pm 0.046)E_s \qquad (2)$$
$$N = 5;\ R = 0.93;\ SD = 0.058$$

In calculations the E_s constants were taken for the RCH_2-series. The obtained dependence (2) favors the conc-

Table 2

Rate Constants and Activation Parameters of Reaction of R"OCOCl Alkyl Chloroformates with 2-Aminoethanol in Ethanol

R"	T, °C	k, $l \cdot mol^{-1} \cdot s^{-1}$	$\Delta H^{\neq}$, kJ/mol	$-\Delta S^{\neq}$ J/mol·K
CH_3	-25	3.5 ± 0.2		
	-10	10.3 ± 0.4	37 ± 1	84 ± 1
	0	19.9 ± 0.7		
C_2H_5	20	4.95 ± 0.18		
i-C_3H_7	20	1.51 ± 0.02		
$C_2H_5OCH_2CH_2$	20	12.6 ± 0.2		
Cl_3CCH_2	-20	58 ± 2		
	-10	118 ± 2	35 ± 1	70 ± 1
	0	215 ± 7		

lusion about a significant contribution of the addition stage (the formation of intermediate (1)) to the process. The electrophilicity of the carbonyl C-atom increases with the strengthening of the substituent's electron-accepting properties thus accelerating the nucleophilic attack. Respectively, an increase in the substituent volume inhibits the process. The response of the structural changes in in chloroformates is lower than that in amine variation. The reaction between the chloroformates and aromatic amines and pyridines[4,9] is found to have analogous effects.

For the reactions between chloroformates and aromatic amines the influence of medium effects has been investigated in detail[1], exclusively aprotic dissolvents were examined. Taking into account the aforesaid, it seemed interesting to estimate the medium factor influence for aliphatic amines in hydroxylic dissolvents series. So, the reaction rate between 2-propyl chloroformate and 2-aminoethanol in aqueous medium and ROH alcohols was measured (Table 3).

Table 3

Rate Constants of 2-Propylchlorophormate Reaction with 2-Aminoethanol in ROH

R	T, °C	k, $l \cdot mol^{-1} \cdot s^{-1}$
H	6	0.101 ± 0.002
	11	0.195 ± 0.004
	15	0.250 ± 0.003
	20	0.416 ± 0.009
	25	0.658 ± 0.008
CH_3	20	0.982 ± 0.001
C_2H_5	20	1.514 ± 0.001
i-C_3H_7	20	1.341 ± 0.003

For the reactions in aqueous medium the activation parameters are $\Delta H^{\neq}$ = 65±1 kJ/mol; $\Delta S^{\neq}$ = -30±5 J/(mol·K), these values are visibly higher in comparison with the corresponding values in ethanol (Tables 1,2). With the exception of 2-propanol the reaction rate increases with a growth in the molecularity of the dissolvent. The dependence of

log k on the Koppel-Palm equation parameters[7] and the analysis of the inductive and steric Taft constants proved that the best correlation was evoked with the medium basicity parameter:

$$\log k = -(1.424 \pm 0.048) + (0.00677 \pm 0.00023) \cdot B \qquad (3)$$

$$N = 4;\ R = 0.99;\ SD = 0.0011$$

In the examined substituent series (H + i-C_3H_7) a lot of parameters ($Y, P, E, B, \sigma^*, E_s$) are correlated. Nevertheless, the obtained equation (3) does not seem a random one though it should be treated carefully. Undoubtedly, the medium basicity affects the reaction rate. Apparently, this influence is caused by the destruction of intramolecular association of 2-aminoethanol. The intramolecular association is accomplished on the account of the interaction between an undivided N-atom electron pair and hydroxyl proton[10], which leads to the nucleophilic decrease. The intramolecular association destruction can also be accomplished by electrophilic solvation, but apparently, the nucleophilic solvation effect is stronger.

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TEMPERATURE DEPENDENCE OF KINETIC ISOTOPE EFFECTS DURING OXIDATION OF BNAH QUINONES

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On oxidation of N-benzyl-1,4-dihydronicotiamide (BNAH) by p-quinones (0.02 M phosphate, pH 7.0) the logarithms of rate constants linearly depend on the single electron reduction potential (E_7^1) of quinones. The reactivity of o-quinones is almost 2 orders higher. In the oxidation of /4,4-$^2H_2$/BNAH the kinetic isotope effects decrease with increasing E_7^1 of quinones. The equal activation energies of the oxidation of BNAH and /4,4-$^2H_2$/BNAH by p-quinones show strong evidence for a "parallel" transition state. In the reaction with o-quinones the activation energy of /4,4-$^2H_2$/BNAH oxidation is higher than that of BNAH, which indicates a different transition state geometry or tunnelling effects.

Quinoidal compounds are widely used in studying the oxidation of reduced nicotinamide adenine dinucleotide (NADH) - a oofactor of dehydrogenases and its analogues[1-9]. It was stimulated by both well-studied thermodynamics of a single- and two-eleotron reduction of quinones[10,11] and searching for effective systems of chemical and electrocatalytical regeneration of cofactors[12]. The majority of experimental data indicates a multi-stage (e^-,H^+,e^-, or $H^\cdot$,e^-) transfer of hydride-ion in this reaction accompanied by a possible formation of charge transfer complexes or ion-radical pairs as intermediate compounds[1,6,8,9]. Moreover, it was found that the reactivity of o-quinones was much more higher than that of p-quinones possessing the same redox potentials[2,3,6], but no explanation has yet been given to this fact.

Semiempirical calculations on temperature dependence of the kinetic isotope effect on the oxidation of dihydropyridines give some information about transition state geometry. Based on the data, a "parallel" or "linear" transition state as well as tunnelling of hydride-ion or some other form of hydrogen may be defined in this reaction[5, 13-15].

In this paper we describe a different pattern of temperature dependence of the kinetic isotope effect on the oxidation of N-benzyl-1,4-dihydronicotinamide (BNAH) by o- and p-quinones in an aqueous medium.

EXPERIMENTAL

BNAH and /4,4-$^2H_2$/BNAH were synthesized as in[9], the deuteration extent of /4,4-$^2H_2$/BNAH, determined by NMR, was not less than 97 %. 2,5-Dibromo-1,4-benzoquinone was synthesized according to a well-known method[2]. 2,5-Dimethyl-1,4-benzoquinone (Sigma, USA), 5-oxy-1,4-naphthoquinone (Aldrich, USA) and 5,8-dioxy-1,4-naphthoquinone (Fluka AG, Switzerland) were used as received. 1,4-Benzoquinone, 2-methyl-1,4-benzoquinone, sodium 1,2-naphthoquinone-4-sulphonate, 1,2-naphthoquinone and 9,10-phenanthrene quinone (pure) were purified by recrystallization from ethanol or benzene or by sublimation in vacuum. Kinetic measurements were carried out in a 0.02 M K-phosphate buffer solution at pH 7.0, containing 1 mM EDTA and in some cases with 20 or 50 % (v/v) of acetonitrile. The reaction was monitored according to fluorescence decrease at 450 nm (excitation wavelength 350 nm). A MPF-4 spectrofluorimeter (Hitachi, Japan) was used in this work. The concentration of BNAH was 5-30 μM and that of an oxidizer (1,4-benzoquinone, 2-methyl-1,4-benzoquinone, 2,5-dimethyl-1,4-benzoquinone, 5-oxy- and 5,8-dioxy-1,4-naphthoquinone, 1,2-naphthoquinone and 9,10-phenanthrene quinone) - 5-30 times higher. The reaction rate was corrected by the BNAH hydration rate, which was

estimated to be $7.0 \cdot 10^{-5}$ s^{-1} (0.02 M phosphate, 25 °C, E_a = = 11.9 kcal·mole^{-1})which is close to that obtained in[5]. In the solutions containing 20 or 50 % acetonitrile the hydration rate was $3.5 \cdot 10^{-5}$ and $2.2 \cdot 10^{-5}$ s^{-1} and activation energy - 12.6 and 13.3 kcal·mole^{-1}, respectively. The reactions were carried out under aerobic conditions. The activation parameters were calculated on the basis of the results obtained in 9-11 measurements over the temperature interval 15-55 °C. Anaerobic oxidation of BNAH by quinones was carried out at 25±0.1 °C using a Hitachi-557 (Japan) spectrophotometer according to a stopped-flow method. The reaction rate of BNAH with 2,5-dibromo-1,4-benzoquinone was monitored by the decrease of BNAH (50 μM) absorption at 350 nm. In the reduction of 1,2-naphthoquinone-4-sulphonate, 1,2-naphthoquinone and 9,10-phenanthrene quinone the rate was estimated by the absorption decrease of 50-100 μM quinone at 400-450 nm. In studying oxidizers about 5-7 experiments have been made at various concentrations of reagents. Oxygen was removed by bubbling the solution for 25-30 min with argon. Data processing was done on a Mera-664 (Poland) computer.

RESULTS AND DISCUSSION

Under aerobic conditions when the oxidizer was used in great excess the concentration of BNAH decreased according to the first order, and the data linearized in semilogarithmic coordinates up to a 85-90 % conversion. The calculated pseudofirst-order rate constants linearly depended on the oxidizer concentration. Similar data have been obtained in anaerobic spectrophotometrical measurements. Thus, on the analogy of numerous data obtained in[1-9] it is possible to conclude that the oxidation of BNAH by quinones is the second order reaction. The rate constants (k_{ox}) and kinetic isotope effects (k_H/k_D), calculated in the oxidation of /4,4-$^2H_2$/ BNAH, are presented in Table 1. The constants of BNAH oxidation by 1,2-naphthoquinone and 9,10-phenanthrene

quinone, obtained under aerobic conditions, are equal to those determined in an anaerobic medium. This shows that hydrogen peroxide and, probably, the other active forms of oxygen, formed in the reoxidation of reduced low-potential quinones, do not affect the rate of BNAH oxidation, which is in agreement with the well-known data[2,5]. The potentials of a single- (E_7^1) and two-electron (E_7^0) reduction of quinones (standard potentials)[3,10,11] are also presented in Table 1.

Table 1. Oxidation Constants, Kinetic Isotope Effects On the Reactions of BNAH With Quinones (pH 7.0, 25 °C) and redox potentials of quinones

Oxidizer	k_{ox},* $l \cdot mole^{-1}s^{-1}$	k_H/k_D,*	E_7^1, V	E_7^0, V
2-Bromo-1,4-benzoquinone	12700	1.7	0.22	0.30
1,4-Benzoquinone	121 5.5**	2.7 4.6**	0.09	0.29
2-Methyl-1,4-benzoquinone	18.3	2.36	0.01	0.21
2,5-Dimethyl-1,4-benzoquinone	1.85	3.08	-0.08	0.16
5-Oxy-1,4-naphthoquinone	5.0	2.34	-0.09	-0.02
5,8-Dioxy-1,4-naphthoquinone	0.95	3.08	-0.11	-0.06
1,2-Naphthoquinone-4-sulphonate	9700	2.6	-	0.21
1,2-Naphthoquinone	280 107***	3.8 5.8***	-0.08	0.14
9,10-Phenanthrene quinone	74.5 22.3***	6.7 7.0***	-0.12	0.02

*relative standard deviation 0.03-0.05, confidence level 0.95.

**a solution containing 50 % acetonitrile.

***a solution containing 20 % acetonitrile.

As it follows from the data in Table 1, the reaction rate is considerably decreased with addition of acetonitrile. Moreover, in some cases the kinetic isotope effect is markedly increased. Table 2 summarizes the activation parameters of BNAH and /4,4-$^2H_2$/BNAH oxidation (E_a^H and E_a^D) as well as preexponential factors (A^H and A^D), calculated by linearization of the data on temperature dependence in Arrhenius coordinates. As in the case of NADH oxidation in an aqueous medium[6], the data on the enthalpy and entropy of activation indicate that a more negative entropy of activation (~-35 cal·mole^{-1}·K^{-1}) is characteristic of p-quinones than that of o-quinones (~-30 cal·mole^{-1}·K^{-1}).

As is seen from our data, a linear increase in the k_{ox} logarithms of p-quinones and a decrease in k_H/k_D are observed on increasing E_7^1 (Fig. 1). It agrees satisfactorily with a three-step transfer of hydride-ion in the oxidation of BNAH[1,8]

$$Q + BNAH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} Q^{-\cdot} \ldots BNAH^{+\cdot} \xrightarrow{k_2} QH^{\cdot} \ldots BNA^{\cdot} \xrightarrow{\text{fast}} QH^- + BNA^+ \qquad (1)$$

where Q is quinone. In this case $k_{ox} = k_1k_2/(k_{-1} + k_2)$. The ratio k_1/k_{-1} is determined by the difference in the potentials of redox pairs $Q/Q^{-\cdot}$ and $BNAH^{+\cdot}/BNAH$. For a number of quinones used k_2 and the kinetic isotope effect in this step must not vary greatly due to strong exothermic transfer of protons[16] (pK_a of $BNAH^{+\cdot}$ equals -3.5- -4.0[17] and pK_a of p-semiquinones - 2.1 - 4.6[10,11]). At sufficiently low k_1/k_{-1} (low E_7^1 for quinone) k_{ox} becomes equal to k_1k_2/k_{-1} and, consequently, the kinetic isotope effect of this reaction reaches its maximal value. Comparison of our results to that obtained for the reactions in acetonitrile[1,8] reveals that the reactivity of quinones in water is significantly higher than that of acetonitrile or water-acetonitrile mixtures (Table 1), and the kinetic isotope effects are lower. Evidently, this may be attributed to increased endothermicity of the first electron transfer (Eq. 1) in acetonitrile. Thus,

Table 2. Activation Parameters Of $BuAH$ Oxidation By Quinones (pH 7.0, 0.02 M phosphate)

Oxidizer	E_a^H, kcal·mole^{-1}	E_a^D, kcal·mole^{-1}	$E_a^D - E_a^H$, kcal·mole^{-1}	A^H, l·mole^{-1}s^{-1}	A^D, l·mole^{-1}s^{-1}	A^H/A^D
1,4-Benzoquinone	4.9±0.1	4.85±0.15	±0.22	$(4.9\pm0.8)\cdot10^5$	$(1.8\pm0.4)\cdot10^5$	3.2±1.1
1,4-benzoquinone*	7.4±0.2	7.7±0.2	0.2±0.26	$(1.4\pm0.4)\cdot10^6$	$(4.6\pm1.6)\cdot10^5$	3.4±1.4
2-methyl-1,4-benzoquinone	5.6±0.2	5.7±0.1	±0.22	$(2.4\pm0.9)\cdot10^5$	$(1.2\pm0.4)\cdot10^5$	2.6±1.0
5-oxy-1,4-napnthoquinone	7.6±0.4	7.4±0.35	±0.25	$(2.2\pm1.1)\cdot10^6$	$(6.2\pm2.7)\cdot10^5$	2.7±1.0
1,2-naphthoquinone	5.4±0.2	6.5±0.2	1.0±0.15	$(3.1\pm1.0)\cdot10^6$	$(3.9\pm0.9)\cdot10^6$	0.77±0.2
1,2-naphtho-quinone	6.2±0.2	7.9±0.4	1.7±0.4	$(3.7\pm1.4)\cdot10^6$	$(1.2\pm0.7)\cdot10^7$	0.45±0.3
9,10-phenanthrene quinone**	7.0±0.2	9.2±0.3	2.2±0.3	$(2.7\pm0.8)\cdot10^6$	$(1.7\pm0.7)\cdot10^7$	0.2±0.8

*a solution containing 50 % acetonitrile

**a solution containing 20 % acetonitrile

the difference in E^1 for the redox pairs benzoquinone/benzosemiquinone and $BNAH^{+\cdot}/BNAH$ in an aqueous medium is equal to -0.84- -0.96 V[7,10,17] and in acetonitrile - -1.06 V[1,8].

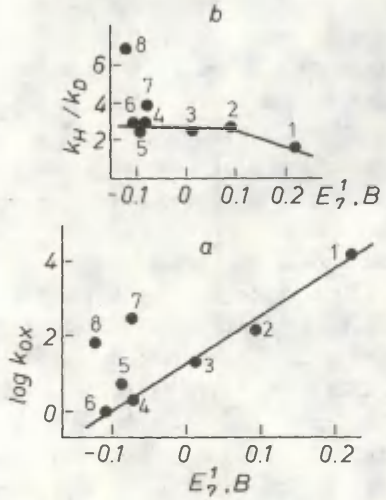

Fig. 1. Dependence of the BNAH oxidation rate constant (a) and kinetic isotope effect (b) on the single-electron reduction potential of quinones: 2,5-dibromo-1,4-benzoquinone (1), 1,4-benzoquinone (2), 2-methyl-1,4-benzoquinone (3), 2,5-dimethyl-1,4-benzoquinone (4), 5-oxy-1,4-naphthoquinone (5), 5,8-dioxy-1,4-naphthoquinone (6), 1,2-naphthoquinone (7), 9,10-phenanthrene quinone (8), pH 7.0, 0.02 M phosphate, 25 °C.

Since the number of o-quinones with estimated E_7^1 is scanty, the analysis of reactivity with the use of this parameter is difficult. However, one can expect that E_7^1 for 1,2-naphthoquinone-4-sulphonate is higher than that of 1,2-naphthoquinone (Table 1). Thus, it is possible to suggest

that the correlation between k_{ox}, k_H/k_D of o-quinones and E_7^1 is similar to that of p-quinones even over a wider range of potentials. It is evident, that the reactivity of o-quinones is by a factor of 2 higher than that of p-quinones at the same potential values (Fig. 1).

On the basis of the temperature dependence of the primary kinetic isotope effects on the oxidation of 1,4-dihydropyridines it was assumed that equal activation energies and A^H/A^D of 2.5-6.0 correspond to a "parallel" transition state (a charge transfer complex with a curved hydrogen transfer pathway)[5,13-15] and $E_a^D - E_a^H = 1.2$ kcal·mole^{-1} and $A^H/A^D = 0.7$-2.5 - to a "linear" hydrogen transfer between a donor and acceptor. Hydrogen tunnelling is supposed when $E_a^D - E_a^H = 1.5$-6.0 kcal·mole^{-1} and $A^H/A^D \leq 0.6$.

Despite the fact that k_H/k_D, presented in this work, are affected to some extent by the secondary effects, the data in Table 2 may be considered as activation parameters of the primary effects, since the temperature dependence of the secondary ones is negligible[5,18]. Hence it follows that the oxidation of BNAH by p-quinones is characterized as a "parallel" transition step (Table 2) which is consistent with the formation of a charge transfer complex as an intermediate of this reaction[1,8]. The transition state of the BNAH oxidation by o-quinones may be formally described as "linear" (Table 2), i.e. a charge transfer complex is absent. However, it is well-known that o- and p-quinones form the analogous charge transfer complexes with aromatic donors, exhibiting similar stability constants and absorption maxima[19,20]. For this reason a less effective complex formation of o-quinones with BNAH is hardly possible. Secondly, a "linear" transition step is merely characteristic of 1,4-dihydropyridine oxidation by positively charged hydride acceptors - methylene blue[5] and N-alkylpyridine derivatives[13-15]. This may be attributed to repulsion of positively charged π-systems of an oxidizer and reducer in the transition state after a partial transfer of hydride-ion[5,13-15]. However, irrespectively of the mechanism of hydride-ion transfer in the oxidation of BNAH by quinones

the charges of reagents in the transition state remain opposite. On the other hand, the values of E_a^H, exceeding E_a^H, are also characteristic of a number of intramolecular rearrangements involving a nonlinear hydrogen transfer. This may be explained in terms of tunnelling effects or the influence of vibrational movement of neighbouring atoms or groups on the transition state energetics[21]. The latter effects may determine an abnormal temperature dependence of kinetic isotope effects and an increased reactivity of quinones. The results concerning fast (10^{10} s^{-1}) intramolecular exchange of hydrogen in protonated o-semiquinones suggest that the participation of neighbouring carbonyl groups in hydrogen acceptance is feasible[22].

The authors thank J.J. Straukas for synthesis of BNAH and 2,5-dibromo-1,4-benzoquinone.

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A STUDY OF DECOMPOSITION KINETICS OF MEISENHEIMER σ-COMPLEXES IN TETRAHYDROFURAN-ALCOHOL MIXTURES

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Spectrophotometric study of the decomposition kinetics of 1,1-dimethoxy-2,4,6-trinitrocyclohexadienate-2,5-sodium in the mixtures of low-polarity solvent tetrahydrofuran (THF) with a series of aliphatic alcohols has shown that the acidity of the protonic component has a major effect on the proton component. Both solvated ions and ion pairs whose concentrations are growing with an increase in the low-polarity tetrahydrofuran content take part in the process. It has been established that the reactivities of the σ-complex's ion pairs exceed those of solvated anions.

In resent years research into the medium effect on the kinetics and mechanisms of reactions has increasingly been in the center of attention in the field of activated nucleophilic substitution. It has been established that the rates of both steps - connection of nucleophilic agent to substrate and decomposition of the formation of σ-complexes remarkably depend on the solvent's composition and properties (see[1-5]).

The present study was aimed at investigation of the kinetics of the 1,1-dimethoxy-2,4,6-trinitrocyclohexadienate-

2,5-sodium (the Meisenheimer σ-complex) decomposition in the binary system THF-alcohols of aliphatic series. The molar fractions of the components varied from 0 to 1. Rates of the reactions were measured spectrophotometrically according to the increase in the optical density of the solution at its short-wave maximum. The latter can be identified as having a weak absorption intensity of the σ-complex. The linear dependences obtained in the coordinates of the logarithms of optical density and time evidence that in this case decomposition obeys the first order reaction kinetics as concerns the σ-complex studied here. The stability of the rate constant in the case of variation of the concentration of the colored product refers also to the aforesaid. The data can be found in Table 1.

The analysis of the results shows that addition of alcohols to THF accelerates the decomposition of the σ-complex. The effect weakens as follows:

butanol < propanol < ethanol < methanol.

As it was shown in[2,3], in the binary mixed solvent (aprotic - proton-donor) the decomposition of anionic σ-complexes is initiated by the protic component, which forms a specific solvating medium and participates in the reaction as an attacking agent. For the Meisenheimer complex this bimolecular process can be expressed by the scheme:

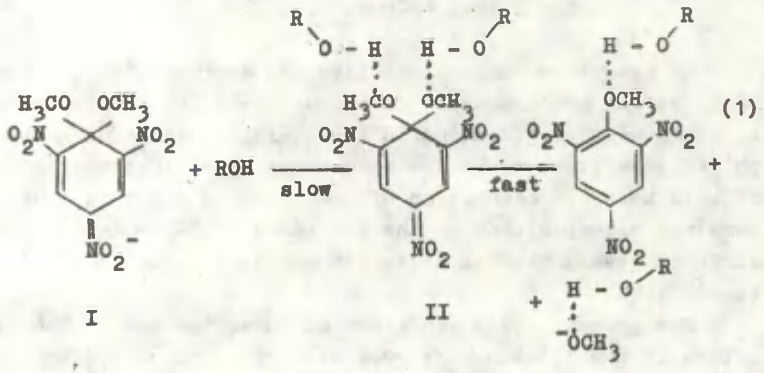


Table 1

Dependence of Decomposition Rate of the Meisenheimer σ-Complex on Composition of Mixed Solvent THF-Alcohols

ROH	DP[7]	pK_a[7]	% ROH	0	10	20	30	40	50	60	70	80	90	100
CH_3OH	32.6	15.09	N_{ROH}	0	0.18	0.33	0.46	0.57	0.67	0.75	0.82	0.89	0.95	1.00
			$k \cdot 10^5, s^{-1}$	0.34	2.04	7.21	15.1	27.5	46.8	50.3	75.4	98.0	131.5	180.0
C_2H_5OH	24.3	15.93	N_{ROH}	0	0.13	0.26	0.37	0.48	0.58	0.68	0.76	0.85	0.93	1.00
			$k \cdot 10^5, s^{-1}$	0.34	0.81	2.76	3.69	10.22	15.8	22.1	37.1	34.2	43.3	46.1
C_3H_7OH	20.7	16.10	N_{ROH}	0	0.12	0.21	0.32	0.42	0.52	0.62	0.72	0.81	0.91	1.00
			$k \cdot 10^5, s^{-1}$	0.34	0.52	0.83	1.37	1.63	2.44	4.29	7.73	12.0	18.95	24.87
C_4H_9OH	17.7		N_{ROH}	0	0.09	0.18	0.28	0.37	0.47	0.57	0.67	0.78	0.89	1.00
			$k \cdot 10^5, s^{-1}$	0.34	0.45	0.56	1.32	1.73	2.32	2.83	5.79	7.15	12.10	19.13

In keeping with that mechanism, in alcoholic solutions the decompostion rate changes in accordance with the acidities of alcohols and depends on the electron-donor properties of their radicals[6]. The correlation dependence found between the logarithm of rate constants (log k) and the σ^*-constant (σ^*) of alkyl groups supports that statement. Studies at various temperatures have shown that activation energy depends rather weakly on the properties of alcohol, the process is controlled by the entropy factor, while the activation entropy for the reaction has negative values[1,6]. The assumption that steric effects make a substantial contribution to the reaction rate has been confirmed by the excellent correlation established between the log k and E_s^c of alkyl radicals of alcohols[6], thus proving the validity of the suggested mechanism.

According to scheme (1) and in keeping with the mass - action law, the rate of the present interaction will increase in the case of a growth in the alcohol concentration in an aprotic solvent. The series of relative effects of alcohols on the stability of the σ-complex is in keeping with their acidities:

$$pK_a\ CH_3OH < pK_a\ C_2H_5OH < pK_a\ C_3H_7OH\ ,$$

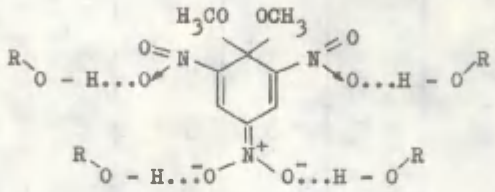
$$15.09 < 15.93 < 16.10\ ,\ \text{respectively.}^{7}$$

At the same time, the dependence of decomposition rate on the molar concentration of the protonic component (Fig.1) sharply deviates from the linear one, which contradicts the expected bimolecularity of the reaction studied. Consequently, participation of some other factors influencing the rate of the process, particularly the medium effects is necessary.

Fig. 2 shows that in the THF mixtures with alcohols the values of the logarithms of reaction rate constants do not depend linearly on the molar fraction within the whole variation range of the relative content of both those solvent components. This fact evidences[8] that the specific solvation of the σ-complex with alcohols plays a significant role

and the effect is more clearly expressed in the case of the lowest homologues.

The formation of specifically solvated particles of type (III) leads to the stabilization of the adduct (I)[9,10], and it is expressed by relative deceleration of its decomposition rate, depending on the addition of the proton-donor solvent to the THF



III

Studies of the electron spectra of the σ-complex (I) in binary mixtures have shown that there takes place a bathochromic shift of a more intense short-wave absorption band during the transition from THF to alcohol (Table 2). The values of the displacement of the absorption maximum ($\Delta\lambda_{max}$) change with variation of the alcohol level in the system and they depend on the properties of alcohol. They go up with the increase in the dielectric constant values. It has already been indicated[11] that in THF the Meisenheimer σ-complex is much less associated, therefore the changes in the absorption spectra that are traced when adding alcohols to THF, can be related with the displacement of ion-pair equilibrium (2) from ion pairs (IV) to free ions (V).

$$\underset{\text{(IV)}}{An^-, M^+} \rightleftharpoons \underset{\text{(V)}}{An^-} + M^+ \qquad (2)$$

Thus, it is evident that the first absorption maximum of the solvated anion is situated in the longwave-length region. The statement is proved by a bathochromic displacement

Table 2

Dependence of Spectral Characteristics of б-Complex (I) on Solvent Composition in System THF-Alcohol (ROH)

ROH	DP[7]	M·g·% ROH λ_{max}	0*	10	20	30	40	50	60	70	80	90	100
CH_3OH	32.6	λ, nm	405	408	413	415	416	416	417	417	417	418	419
		$\Delta\lambda$, nm	00	3	8	10	11	11	12	12	12	13	14
C_2H_5OH	24.3	λ, nm	405	408	410	413	415	416	417	417	417	417	418
		$\Delta\lambda$, nm	0	3	5	8	10	11	12	12	12	12	13
C_3H_7OH	20.7	λ, nm	405	405	405	406	408	409	410	411	413	416	417
		$\Delta\lambda$, nm	0	0	0	1	3	4	5	6	8	11	12
C_4H_9OH	17.7	λ, nm	405	405	405	406	406	407	409	410	412	413	415
		$\Delta\lambda$, nm	0	0	0	1	1	2	4	5	7	8	10
+ crown-ether		λ, nm						419	418	417	417	417	
+ $NaClO_4$		$\Delta\lambda$, nm		404	406	407	405	405	407	407	408		

* - for б-complex in THF in the presence of dibenzo-18-crown-6-ether λ_{max} = 420 nm.

DP - dielectric permittivity

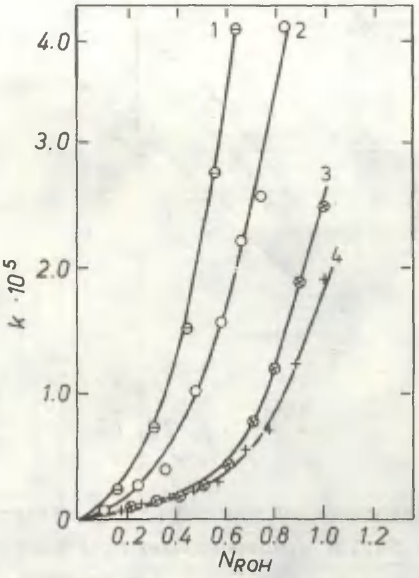


Fig. 1. Dependence of constants of decomposition rate of the Meisenheimer б-complex on the molar concentration of alcohols in THF: 1 - methanol, 2 - ethanol, 3 - propanol, 4 - butanol.

of the spectrum (Table 2) when dibenzo-18-crown-6-ether, which dissolves alkaline cations and consequently, favors division of ions[12] is conducted into the tetrafuran solution of the б-complex (I).

It is known that both free ions and their ion pairs remarkably differ in their chemical activities[13]. Therefore, substantial effects of the equilibrium state of adduct's ionization and the reactivity of its particles on the stability of the studied adduct can be expected. This substantial

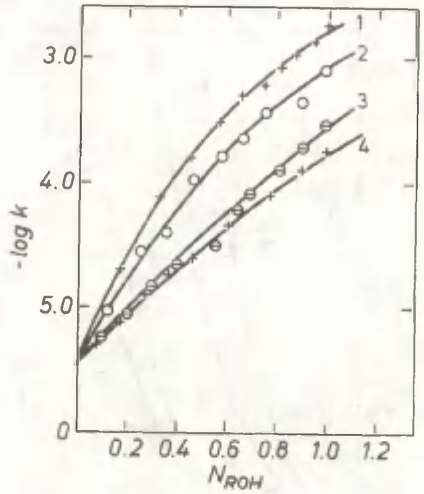


Fig. 2. Dependence of the logarithm of constants of σ-complex decomposition rate in THF: 1 - methanol, 2 - ethanol, 3 - propanol, 4 - butanol

drop in the values of decomposition constants (I) brought about by the increase in the proton component's content in a mixed solvent is probably related to the displacement of equilibrium (2) towards increasing the concentration of free ions (V) which will be dissolved by alcohol molecules. The increase in the contribution of the specifically solvated anions of the σ-complex brings about retardation of the decomposition, which is in keeping with the assumption that their reactivities are poorer than those of the corresponding ion pairs[14].

To support this hypothesis, we studied the effects of ion and solvation additions on the kinetics of the decomposition of the Meisenheimer σ-complex in the system THF-butanol at various compositions of solvent components (Table 3). According to the obtained data we can say that if sodium perchlorate is transferred into the reaction solution, the

Table 3

Effects of Salts and Crown-Ethers on Kinetic and Spectral Characteristics of Meisenheimer σ-Complex

Composition of mixture	C_4H_9OH volume %	50	60	70	80	90
THF	$k \cdot 10^5$, s^{-1}	2.31	2.83	5.79	7.15	12.10
	λ_{max}, nm	407	409	410	412	413
THF	$k \cdot 10^5$, s^{-1}	3.49	4.82	7.45	10.28	14.16
$NaClO_4$	λ_{max}, nm	405	407	407	408	
THF	$k \cdot 10^5$, s^{-1}	1.08	0.98	2.08	4.05	5.19
crown-ether	λ_{max}, nm	419	418	417	417	417

decomposition of the σ-complex will accelerate remarkably, but in the presence of the dibenzo-18-crown-6-ether the process will slow down. Thus, addition of a salt with a similar ion leads to the displacement of the complex toward a higher content of ion pairs. Since the latter are more active than the corresponding anions, the decomposition rate is growing. The introduction of crown-ether that breaks ion associates at the expense of cation binding leads to the stabilization of the adduct. A change in the state of the ions association of the σ-complex depending on definite conditions has also been confirmed by spectral studies in the mixture THF-butanol, during which the absorption maximum was displaced into the longwave region of the spectrum when adding crown-ether and in the presence of sodium perchlorate the band underwent a hypochromic shift (Table 3).

Thus, studies show that in the THF mixtures with protonic solvents, the decomposition of the σ-complex of Meisenheimer is a bimolecular process. Its rate depends on the content of alcohol in the reaction system and its proton-do-

nor properties. Specific solvation of the complex by a protonic component of the binary solvent and the ion association of the adduct in low-polarity media complicate the reaction. The statement has been proved valid by spectral and kinetic studies in the presence of crown-ether and salts. The obtained data serve as the evidence for a better reactivity of the ion pairs of the complex compared to its solvated anions.

Experimental

The σ-complex (I) was obtained as described in[15]. The solvents used were purified and dried by well-known methods[16]. The technique of kinetic measurements has been described earlier[17]. The obtained experimental data were processed according to the first-order equation:

$$kt = 2.303(\log D_0 - \log D).$$

In mixed solutions the electron spectra of the σ-complex were recorded on a spectrophotometer Specord UV-Vis. Kinetic measurements were conducted on a spectrophotometer CF-14.

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STUDY OF S_N1 REACTIONS USING VERDAZYLS. IX.* NATURE OF NEGATIVE SALT EFFECT PRODUCED BY HYDROGEN HALIDE SALTS DURING Ph_2CHBr HETEROLYSIS IN ACETONITRILE

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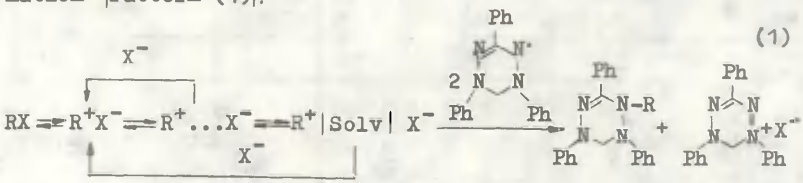
Ph_2CHBr heterolysis rate ($v = k[Ph_2CHBr]$) in the presence of $Et_4N^+Br^-$ and $Et_4N^+I^-$ does not depend on triphenylverdazyl concentration and the nature of its substituent, whereas in the presence of $Et_3PhCH_2N^+Cl^-$ the above factors affect the heterolysis rate. Therefore, the negative salt effect in the first case is supposed to be determined by the influence of salts on space-separated ion pair of the substrate whereas in the latter case this effect is presumably determined by the influence of salt on solvent-separated ion pair.

Our earlier paper of this series[2] showed the additions of chlorides, bromides and iodides to substantially decrease the rate of Ph_2CHBr heterolysis in MeCN. The heterolysis was supposed not to reach the formation of free carbocation and the reaction was presumed to proceed via the intermediate formation of intimate and solvent-separated ion pair, rapidly and quantitatively reacting with triphenylverdazyls (Y-Vd$^\bullet$), used as internal indicators. Both in the presence of $Et_4N^+Br^-$ and with no salt additions the reaction rate is independent on the nature of the substituent in Y-Vd$^\bullet$. Therefore, there is no competition between nucleophiles

* VIII is reported in [1].

(Y-Vd$^{\cdot}$, salt) for cationide, i.e. the nucleophiles influence on different intermediates. A decrease in the reaction rate could be naturally explained by the salt action on the intimate ion pair which stabilizes as a result of complex formation (quadrupole, ion triplet). However, this formal explanation was difficult to understand.

Comprehensive verdazyl-oriented study of the heterolysis mechanism for a wide range of organic substrates (t-BuX, 1-AdX, p-$MeOC_6H_4CCl_3$, PhCHClMe, 7-α-bromcholisterylbenzoate, p-$MeOC_6H_4CHCl_2$, Ph_2CCl_2[3-8]) led us to the conclusion that the conversion of the intimate ion pair into the solvent-separated one proceeded through the formation of a space-separated ion pair (rate-determining step). The negative salt effect is related to the effect of the salt on a solvent- or space-separated ion pair with further covalent substrate formation [Pattern (1)].



(1)

Pattern (1) refers to a salt with common ion. In this case negative salt effect is determined by the catalytic action of the ion pair external return. At low substrate conversion (our case) this pattern is also true for the salts with uncommon ion - the effect is obtained due to concentration decrease of the product-forming intermediate.

Should the salt act on a solvent-separated ion pair there would be a competition between Y-Vd$^{\cdot}$ and the salt for the cationide and the reaction rate would depend in this case on the concentration and nature of Y-Vd$^{\cdot}$. Should, however, the salt act on a space-separated ion pair, such a dependence would be missing[4,7].

We studied the effect of Y-Vd$^{\cdot}$ concentration and nature on Ph_2CHBr heterolysis in acetonitrile in the presence of $Et_4N^+Br^-$, $Et_4N^+I^-$ and $Et_3PhCH_2N^+Cl^-$ at 25°C. 1,3,5-triphenylverdazyl (Vd$^{\cdot}$), 1-phenyl-3,5-di-(4- methoxyphenyl)ver -

dazyl[$(MeO)_2$-Vd$^\bullet$] and 1,5-diphenyl-3-(4-nitrophenyl)verdazyl (NO_2-Vd$^\bullet$) were used as indicators. Y-Vd$^\bullet$ concentration in kinetic tests was ~100 times lower than that of Ph_2CHBr and the substrate conversion was ~ 0.1 %.

Similar to that without salt additions[1] the reaction rate constant was calculated using the kinetic equation (2)

$$v = k[Ph_2CHBr] \qquad (2)$$

The Table given below shows conditions and results of kinetic tests.

Table

Ph_2CHBr Heterolysis Kinetics in MeCN in the Presence of Salts at 25°C

$[Ph_2CHBr]\cdot 10^3$, mole/l	Y-Vd$^\bullet$	$[Y\text{-}Vd^\bullet]\cdot 10^4$, mole/l	Salt; $c_0\cdot 10^4$, mole/l	$k\cdot 10^7$, sec^{-1}	$k\cdot 10^7$, sec^{-1}, average
1	2	3	4	5	6
9.49	Vd$^\bullet$	0.709	$Et_4N^+Br^-$; 3.11	9.53	9.75±0.22
9.48		2.57	$Et_4N^+Br^-$; 3.11	9.75	
9.46		2.59	$Et_4N^+Br^-$; 3.11	9.96	
9.45	NO_2-Vd$^\bullet$	0.880	$Et_4N^+Br^-$; 3.11	9.62	9.64±0.02
9.41		3.35	$Et_4N^+Br^-$; 3.11	9.66	
9.42	$(MeO)_2$-Vd$^\bullet$	0.637	$Et_4N^+Br^-$; 3.09	9.60	9.50±0.05
9.08		1.32	$Et_4N^+Br^-$; 3.09	9.52	
9.53		1.28	$Et_4N^+Br^-$; 3.09	9.49	
9.36		2.68	$Et_4N^+Br^-$; 3.09	9.45	
9.35		2.68	$Et_4N^+Br^-$; 3.09	9.46	
9.56	Vd$^\bullet$	1.66	$Et_4N^+I^-$; 3.12	14.0	13.9±0.5
9.51		0.847	$Et_4N^+I^-$; 3.12	14.6	
9.68		2.56	$Et_4N^+I^-$; 3.12	13.1	
9.28	NO_2-Vd$^\bullet$	0.530	$Et_4N^+I^-$; 3.09	9.50	11.7±1.1
9.63		1.11	$Et_4N^+I^-$; 3.09	11.9	

1	2	3	4	5	6
9.52 9.67	NO_2-Vd·	1.52 2.40	$Et_4N^+I^-$; 3.12 $Et_4N^+I^-$; 3.09	12.5 12.8	11.7±1.1
9.72 9.66 9.61	$(MeO)_2$-Vd·	1.08 1.94 3.30	$Et_4N^+I^-$; 3.10 $Et_4N^+I^-$; 3.10 $Et_4N^+I^-$; 3.12	13.40 13.40 13.40	13.40±0.0
9.46 9.45 9.47 9.45	$(MeO)_2$-Vd·	0.872 0.848 1.66 3.07	$Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11	6.03±0.10 6.03±0.11 6.23±0.10 6.66±0.20	
9.40 9.43 9.36 9.39 9.43	Vd·	0.711 0.777 1.58 1.56 2.79	$Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11	7.40±0.11 7.55±0.09 8.43±0.12 8.40±0.10 9.18±0.09	
9.46 9.45 9.42 9.40	NO_2-Vd·	0.906 1.68 1.75 3.29	$Et_3PHCH_2N^+Cl^-$; 3,11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11 $Et_3PhCH_2N^+Cl^-$; 3.11	7.96±0.12 9.07±0.08 9.09±0.07 10.8±1.0	

In the presence of $3.1 \cdot 10^{-4}$ mole/l $Et_4N^+Br^-$ and $Et_4N^+I^-$ the values of k do not depend upon Y-Vd· concentration and the nature of its substituent - for the first salt $k_{25} = (9.58 \pm 0.11) \cdot 10^{-7}$ sec^{-1}, for the second - $k_{25} = (13.2 \pm 0.6) \cdot 10^{-7}$ sec^{-1}. Consequently, the negative salt effect of these salts (without the addition of the salt giving $k_{25} = 25 \cdot 10^{-7}$ sec^{-1})[2] is determined by the salt reaction with a space-separated ion pair.

In the presence of $Et_3PhCH_2N^+Cl^-$ the reaction rate depends both on the verdazyl concentration and the nature of its substituent. The difference of values is small, but the quantitative difference in comparison with previously tested salts is doubtless. This is fairly well seen in the figure

(k value without salt additions is shown by a dotted line). The negative salt effect of the chloride is determined by the reaction between the salt and solvent-separated ion pair.

Similar dependences were observed earlier during the heterolysis of 1-adamantylpicrate (1-AdOPic) in propylene carbonate and γ-butyrolactone[7] and 1-AdOTs in propylene carbonate - a decrease in the reaction rate in the presence of $Et_4N^+Br^-$ was determined by the reaction of the salt with either space-separated or (in the presence of $Et_4N^+Cl^-$) solvent-separated ion pair. As opposed to the above, during the heterolysis of 1-AdOTs in γ-butyrolactone both salts react with the solvent-separated ion pair. In adamantyl substrates the nucleophilic attack of the intimate ion pair by the salt is precluded due to steric hindrance. The lack of competition between Y-Vd$^\cdot$ and the salt during the heterolysis of these compounds was one of the reasons explaining the introduction of a space-separated ion pair into the Winstein equation. Similarity of effects seems to be an evidence that in Ph_2CHBr case the heterolysis proceeds along the same path.

The figure shows that in the presence of $Et_3PhCH_2N^+Cl^-$ the reaction rate is described by a summarized kinetic equation:

$$v = k_0 + k_2[Ph_2CHBr][Y\text{-}Vd^\cdot] \qquad (3)$$

This equation has no physical meaning since the reaction rate, determined against verdazyl consumption, at $[Y\text{-}Vd^\cdot] \to 0$ should also tend to zero rather than to k_0. Consequently, at low indicator concentration the curve of k vs. $[Y\text{-}Vd^\cdot]$ should have a deflection (no experimental confirmation was found) and following the deflection $k \to 0$ at $[Y\text{-}Vd^\cdot] \to 0$. Similar picture was observed earlier during the heterolysis of 1-AdOTs in MeCN[7] in the presence of $Et_4N^+Cl^-$ and during the solvolysis of Ph_2CCl_2 and $p\text{-}MeOC_6H_4CHCl_2$ in aqueous dioxane[8]. This is determined by the change of the rate-determining steps - at relatively high concentrations of Y-Vd$^\cdot$ a cationide is formed at the rate-determining step (S_N1 reaction) and k vs. $[Y\text{-}Vd^\cdot]$ relation is determined in this case by a competition between the salt and verdazyl for the inter-

mediate, whereas at low indicator concentrations the solvent-separated ion pair interacts with Y-Vd$^{\bullet}$.

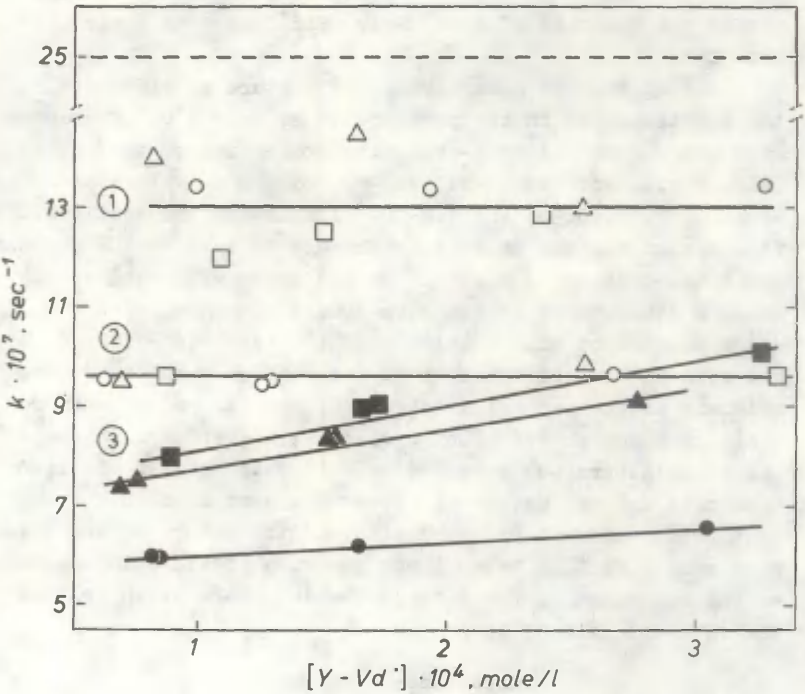


Fig. The effect of Y-Vd$^{\bullet}$ concentration and nature on Ph_2CHBr heterolysis rate in the presence of salts, 25°C

—— k value without salt additions

1 - $Et_4N^+I^-$, 2 - $Et_4N^+Br^-$, 3 - $Et_3PhCH_2N^+Cl^-$

▲ △ - Vd$^{\bullet}$; ● ○ - $(MeO)_2$-Vd$^{\bullet}$; ■ □ - NO_2-Vd$^{\bullet}$

The reaction of Y-Vd$^{\bullet}$ with solvent-separated ion pair seems to proceed via electron transfer from verdazyl to cationide as it is observed during the reaction of verdazyl with $PhN_2^+BF_4^-$ ion pair[9]. The rate of the latter depends on the concentration values of both reagents raised to the first power increasing with an increase in electron-donating properties of the radical. Similar regularities were observed during the reaction of 1-$Ad^+|Solv|OPic^-$ and 1-$Ad^+|Solv|OTs^-$ with Y-Vd$^{\bullet}$[7].

During Ph_2CHBr heterolysis the picture is different - the reaction rate in the presence of $Et_3PhCH_2N^+Cl^-$ increases with increasing electron-accepting properties of the radical (viz. Fig.). For (MeO_2)-Vd$^{\bullet}$-Vd$^{\bullet}$-NO_2-Vd$^{\bullet}$ the k_2 values are equal to 0.17, 0.90, and $1.2 \cdot 10^{-3}$ l/mole·sec, respectively. This speaks for the multi-stage nature of Y-Vd$^{\bullet}$+$Ph_2CH^+|Solv|Br^-$ reaction. Complex seems to be formed first with verdazyl being a donor, then at the rate-determining step either a decomposition of this complex with the formation of $Ph_2CH^{\bullet}$ and $Y\text{-}Vd^+Br^-$ or the reaction of the complex with the second molecule of the radical is observed. The last stage must reveal the electron-accepting properties of verdazyl in complex which determines observed relationship between the reaction rate and the nature of the substituent in Y-Vd$^{\bullet}$.

Thus, verdazyl-oriented study of the nature of the negative salt effect in heterolysis reaction provides information on the mechanism of the product-forming stage which follows the rate-determining step.

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INFLUENCE OF INHIBITORS ON INITIATION OF THE GRIGNARD REACTION. NATURE OF INDUCTION PERIOD

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The induction period of the reaction of n-butyl bromide with metallic magnesium in diethyl ether and in toluene with additions of diethyl ether was investigated in presence of the following inhibitors: water, deuterium oxide, methanol, ethanol, 1-butanol, 1-octanol, stearic acid, and anthracene. Inhibition of the Grignard reaction does not consist in capture of free radicals but inhibitors react with a Grignard reagent that cleans the surface of magnesium metal during the induction period. Products of the reaction with inhibitors influence the induction period differently.

1. Introduction

Everyone who has dealt with preparing of a Grignard reagent has probably experienced that the reaction between metallic magnesium and organic halide does not begin immediately but only after a certain induction period. It is known that[1] the duration of the induction period can greatly vary under the influence of activators and inhibitors. The most well-known inhibitor - water, is found in nearly all the solvents that can be used for preparation of Grignard reagents. It has been shown that additions of water

prolong induction period, and in the presence of a critical concentration of the inhibitor the reaction does not start at all[2-6]. Besides water, inhibitory influence has been ascertained in case of oxygen[2], peroxides[6], and other possible admixtures in reagents and solvents. It was found that after removal of water the reaction started immediately[2,3,5,7]. A reaction of a small portion of alkyl halide with magnesium was used in order to eliminate the induction period in kinetic investigations[8,9]. After adding another portion of the reagent the reaction begins without any induction period. Induction period was also absent in a gas-phase reaction with a sublimed film of magnesium metal[10].

It follows that the induction period is not connected with the reaction mechanism but is caused by removable factors[9]. There is no unanimous comprehension of the nature of induction period. It has been assumed that for initiation of the reaction it is necessary to clean the surface of magnesium from oxides[11]. This can be achieved either by a reaction with a Grignard reagent and an initiator (e.g., with iodine) or using ultrasonication[12]. The inhibitory role of water has been considered as a purely physical one which can be removed either chemically[3] or by means of sonication[13]. On the other hand, it has been supposed[6,9] that water and other inhibitors capture the free radicals produced by the reaction. The chain reaction of organomagnesium compound formation can only evolve after the inhibitor is totally consumed.

Only a few quantitative investigations of the induction period have been published. It was mainly the duration of the induction period in presence of different additions of water[2,4,6] and peroxides[6] that was determined in comparison to the induction period in pure ether. We undertook a detailed examination of the induction period involving a large variety of inhibitors. The reaction of n-butyl bromide with magnesium in diethyl ether and in toluene with additions of diethyl ether was chosen for a model process.

2. Determination of Characteristics of the Induction Period

The course of the Grignard reaction is well described in the papers by Hořak and Soogenbits[6]. This is also schematically represented in Fig. 1. As the induction period, one can take time (t_i'), required for obtaining a certain measurable concentration of the product (c_i'), time, corresponding to the point of maximum curvature on the kinetic curve[15] (t_i''), or the starting time of the most rapid process[6] (t_i'''). Evidently, it is difficult to specify the induction period, even more so to determine its duration with a sufficient precision.

Kilpatrick and Simons determined the induction period from the point where a semilogarithmic anamorphosis of the kinetic curve intersected the time axis[11]. Gilman and Vanderwal[2] considered the induction period to be the time of appearance of a Grignard reagent by the Gilman color-test[16]. The end of the induction period was also fixed either by the appearance of a turbid layer in the reaction mixture[4], or by a temperature rise[6].

Our method rests on the finding that the coloring of the reaction mixture caused by the iodine added, remained practically unchanged up to the end of the induction period and then disappeared rapidly. Immediately after that or even at the same time visible reaction began (formation of bubbles on the surface of magnesium, sometimes appearance of a slight turbidity). Visually determined induction time proves to be sufficiently well reproducible in parallel measurements ($\pm$ 5 sec on the average).

Although iodine is known as an inhibitor capable of scavenging free alkyl radicals[17], in such experimental conditions it does not evidently appear to be an inhibitor, as it is not consumed during the induction period but after the beginning of a vigorous reaction only. Moreover, iodine is frequently used as an activator of the Grignard reaction[1]. To clarify the activating ability of iodine we carried out several parallel experiments with various ad-

ditions of inhibitors but without iodine. The induction period was prolonged only by 5-10 sec, that might be connected with difficulties in visual determination of the end of the induction period in the absence of iodine. It has to be mentioned that the concentration of iodine in our experiment (0,001 M) was considerably lower than recommended for activation of the reaction[1], e.g., Kilpatrick and Simons[11] considered the optimum concentration to be as high as 0.015 M. Some check experiments have been carried out with the following mixtures: butyl bromide, ether and iodine; butyl bromide, ether, toluene, and iodine; ether, iodine, and magnesium metal; ether, toluene, iodine, and magnesium metal. In no case either disappearance or even any noticeable change in the iodine color was observed during 900 sec.

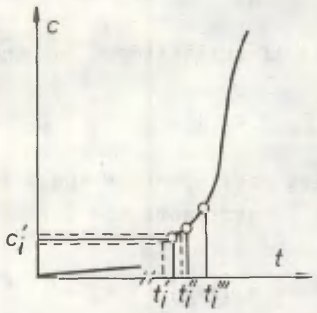

Fig. 1. Schematic course of the Grignard reaction with induction period.

c - concentration of the Grignard reagent

t_i - induction period (see text)

The induction period was determined at 20° C in a test-tube for 10 ml of reaction mixture equipped with a glass stopper and a magnetic stirrer. The weight of magnesium was 0.3 g. The concentrations were: for n-butyl bromide 0.86 M, iodine 0.001 M, inhibitors from 0.003 M to 0.06 M. The details of the experiment are described in section 5.

As it is mentioned in the Introduction, in previous works induction period was determined both in the presence and absence of inhibitors, thereupon the results were collated. To enable a more detailed analysis of the phenomenon of inhibition, we exploited apparent and intrinsic initiation constants.

If an inhibitor reacts with active intermediate particles rapidly enough, the following equation holds practically up to the end of the induction period.

$$-\frac{d[\mathrm{Inh}]}{dt} = W_o ,$$

where W_o denotes the rate of initiation. In the simplest case

$$W_o = k_o[A],$$

where k_o is the initiation rate constant and A is the initiating reagent . In the present work the latter was n-butyl bromide. Hence,

$$[\mathrm{Inh}] = [\mathrm{Inh}]_o - W_o t.$$

By the end of induction period ($t=t_i$) $[\mathrm{Inh}] = 0$. It follows that

$$W_o t_i = [\mathrm{Inh}]_o \quad \text{and} \quad k_o = \frac{[\mathrm{Inh}]_o}{t_i[A]_o} .$$

For the sake of comparability of the results we used an increment of induction period, defined as a difference $t_i - t_i^o$, where t_i^o is the induction period in the absence of added inhibitors. In diethyl ether the mean value of t_i^o

from comparable experiments (similar quantities of alkyl halide and magnesium metal) varied between 56 and 72 sec. Obviously, the initial value of the induction period, t_i^o, corresponds to the period indispensable to clean the magnesium surface from oxides and to capture uncontrolled inhibitors. If this is true, in the first approximation, the increment of induction period is equal to the time required for a total consumption of the added inhibitor.

Evidently, duration of an induction period cannot depend on the nature of the inhibitor. Hence, the initiation constant, k_o, proves to be a characteristic parameter of the reaction system. It can be expressed as follows:

$$k_o = \frac{[Inh]_o}{(t_i - t_i^o)[A]_o}$$

If a dependence of the initiation constant on the nature and initial concentration of the inhibitor is observed, the influence of the inhibitor or its conversion products upon the initiation process can be inferred. In such a case a complicated dependence may appear, and the k_o observed, which was determined from the induction period, may have an integral value with most complicated physical meaning. Undoubtedly, the dependence of the apparent initiation constant on the initial concentration of the inhibitor

$$k_o = \varphi([Inh]_o) ,$$

will be of special interest. Extrapolation of the function to the zero value of the inhibitor concentration must then obtain the value of the intrinsic initiation constant, further denoted by k_o^* .

3. Results and Discussion

3.1. Water in Diethyl Ether.

Induction periods and the corresponding calculated initiation constants for different additions of water and deuterium oxide are presented in Table 1.

A typical dependence of the induction period on the inhibitor concentration is represented in Fig. 2. As it is seen, the induction period increases nonlinearly with increasing additions of water. At a certain critical concentration of water the duration of the induction period practically reaches infinity, i.e., the reaction cannot be initiated any more. The same feature was observed in previous works[4,6]. In terms of apparent initiation constants (see section 2), it reveals a dependence of the latter on the concentration of the added inhibitor (Fig. 3). When the concentration of the inhibitor has approached a critical value, this constant becomes equal to zero. It means that the inhibitor, water in this case, or the products of its conversion, inhibits the initiation process. Simple inhibition by means of trapping active intermediates cannot obviously lead to such relationships.

One can suppose that secondary effects of water inhibition are caused by the products of water reaction. Deposited on the surface of magnesium metal, they can block the reaction centers. So we observed the appearance of a white turbid precipitate in the initial period of the reaction, having also been reported in previous papers[2,4,6]. The composition of the precipitate was found[4] to correspond to formula $MgBrOH \cdot H_2O$. It follows that only one hydrogen atom of water could react.

It is seen in Fig. 3 and also from the data of Table 2, that the dependence of the initiation constant on the initial concentration of water can be well approximated with a straight line. The same figure also shows that the initiation constants obtained from different series of

Table 1

Induction Periods and Initiation Constants in the Presence of Water or Deuterium Oxide in Diethyl Ether

H_2O			D_2O			H_2O[a]		
$c \cdot 10^{2}$[b]	t[c]	$k \cdot 10^{4}$[d]	$c \cdot 10^{2}$[b]	t[c]	$k \cdot 10^{4}$[d]	$c \cdot 10^{2}$[b]	t[c]	$k \cdot 10^{4}$[d]
0	68	-	0	71	-	0	40	-
0.80	90	4.22	0.90	100	3.60	1.22	74	4.16
1.10	110	3.04	1.18	112	3.30	1.61	88	3.89
1.46	135	2.53	1.45	140	2.43	2.00	113	3.18
1.70	150	2.40	1.80	148	2.70	2.37	140	2.77
2.03	176	2.18	2.14	176	2.38	2.81	201	2.02
2.30	232	1.62	2.35	283	1.63	3.18	270	1.60
2.53	360	1.00	2.48	370	0.96			
0	66	-	0	62	-			
1.00	98	3.60	0.89	86	4.30			
1.46	131	2.60	1.40	130	2.40			
2.03	191	1.90	1.80	166	2.00			
2.50	320	1.15	2.20	245	1.40			

a) doubled amount of magnesium metal
b) initial concentration of the inhibitor mole/l
c) induction period, sec
d) initiation constant, sec^{-1}

experiments fairly well lay on a common line. The latter manifests the advantage of the involvement of the increment of induction period and of the apparent initiation constant (section 2). An increase in the weight of magnesium and, consequently, also in its surface area, caused a shortening of the induction period and a shift of the critical value of the inhibitor addition towards higher quantities. However, the doubling of the surface area of magnesium caused an 18% increase in the value of the intrinsic initiation constant, k_0^*, only.

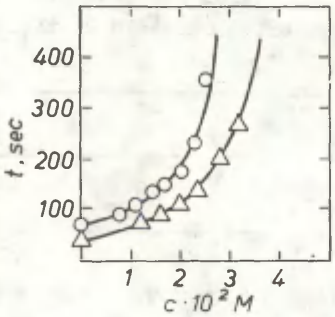

Fig. 2. Depemdence of duration of the induction period on the initial concentration of water in the reaction mixture. ○ - weight of magnesium 0.3 g, △ - weight of magnesium 0.6 g.

Table 2

Results of the Statistical Treatment of Dependences of Apparent Initiation Constants on Initial Concentration of Inhibitor

Inh	$k_0^{\text{эф}} \cdot 10^3$	slope	S	R	n[a]
H_2O	0.510±0.024	-0.0158±0.0012	0.023	0.975	11
D_2O	0.515±0.043	-0.0159±0.0024	0.042	0.914	11
H_2O[b]	0.601±0.038	-0.0136±0.0019	0.036	0.950	6

a) number of points; b) doubled amount of magnesium

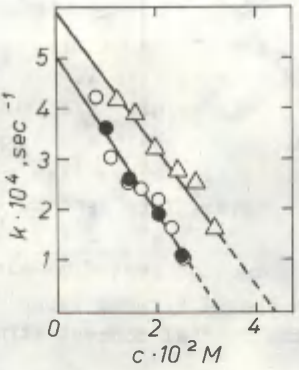

Fig. 3. Dependence of the apparent initiation constant on the initial concentration of water in the reaction mixture. ● ○ - weight of magnesium 0.3 g (two independent series of experiments), △ - weight of magnesium 0.6 g.

Replacement of water by deuterium oxide did not cause any statistically distinguishable alteration in the obtained parameters (Table 2). It is known that for the reactions of organomagnesium compounds with water the kinetic isotope effect is rather small[18], but in reactions with free radicals a considerable KIE should appear. However, there is no reason to expect a KIE in this case because the induction period cannot depend on the nature of an inhibitor. In order to clarify the secondary effects of inhibition we searched for some isotope effects connected with adsorption of the inhibitor. Such effects could not, however, be detected within the accuracy of our experiment.

3.2. Organic Inhibitors in Diethyl Ether.

We have also used aliphatic alcohols of various lengths of carbon chain and stearic acid as inhibitors. The origin of such a choice of inhibitors rests on the assumption that in case the inhibition is caused, even if partially, by adsorption on the surface of magnesium, the inhibitors of different lengths of hydrocarbon chain would exert different influence on the inhibition process. The results were not so straightforward, however, they lead us to some unexpected conclusions.

The results of the induction period measurements are presented in Table 3. In Fig. 4 various dependences of the initiation constant on the initial concentration of the inhibitor are presented.

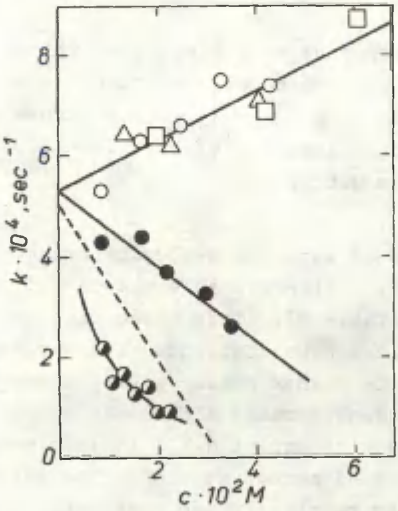

Fig. 4. Dependence of the apparent initiation constant on initial concentrations of inhibitors: ◑ - methanol, ● - ethanol, ○ - n-butanol, △ -n-octanol, □ - stearic acid. Dashed line represents the dependence for additions of water.

Table 3

Induction Periods and Initiation Constants in the Presence of Organic Inhibitors in Diethyl Ether

CH_3OH			C_2H_5OH			$n\text{-}C_4H_9OH$		
$c \cdot 10^{2a}$	t^b	$k \cdot 10^{4c}$	$c \cdot 10^{2a}$	t^b	$k \cdot 10^{4c}$	$c \cdot 10^{2a}$	t^b	$k \cdot 10^{4c}$
0	69	-	0	59	-	0	72	-
1.06	151	1.50	0.80	81	4.30	0.88	91	5.30
1.55	209	1.25	1.70	104	4.38	1.70	103	6.30
2.01	327	0.90	2.20	128	3.70	2.50	116	6.60
2.26	368	0.88	3.00	165	3.28	3.35	124	7.50
0	68	-	3.50	215	2.60	4.30	144	6.90
0.81	112	2.20						
1.30	158	1.67						
1.80	218	1.40						

$n\text{-}C_8H_{17}OH$			$n\text{-}C_{17}H_{35}COOH$		
$c \cdot 10^{2a}$	t^b	$k \cdot 10^{4c}$	$c \cdot 10^{2a}$	t^b	$k \cdot 10^{4c}$
0	64	-	0	56	-
1.38	89	6.40	2.00	95	6.40
2.33	107	6.20	4.20	126	6.90
4.10	131	7.10	6.10	137	8.70

a) initial concentration of the inhibitor, mole/l

b) induction period, sec.

c) initiation constant, sec^{-1}.

It appears that all the investigated substances prolong the induction period but the calculated initiation constants differently depend on the additions of inhibitors. Thus, the progressive admixtures of methanol and ethanol gradually lower the value of the apparent initiation constant. On the contrary, alcohols of longer chains and stearic acid enhance its value. At the same time the points for the latter inhibitors (Fig. 4) in the first approximation lay on a common line with a positive slope. The points for ethanol can be approximated with a straight line of

negative slope and that for methanol with a descending curve. It is worth noting that practically all dependences intersect in a common point at zero addition of the inhibitor. It justifies the involvement of apparent and intrinsic initiation constants (section 2). The value of that point on the ordinate axis can be taken for k_o^{π}.

A common feature of the organic inhibitors under investigation is that the extrapolation of the obtained dependence up to intersection with concentration axis gives a critical admixture of the inhibitor which is greater than for water (see Fig. 4). Consequently, the products of the reaction with alcohols are in ether more soluble than bromomagnesium hydroxide[4] (cf. section 3.1.). Probably, these products are bromomagnesium alcoxides whose solubility should increase with increasing hydrocarbon chain. Besides, the positive slope of the dependence for the substances having long carbon chain directly indicates their promoting action on the initiation. Very likely this is caused by the solubilization of the oxidic film of magnesium surface. It is reported [19] that higher alcohols are able to catalize to some extent the Grignard reagent formation. We observed that when higher alcohols or stearic acid are used the white turbid precipitate whose appearance is quite common in the case of water and lower alcohols, did not form. Hence, we can conclude that higher alcohols do inhibit the Grignard reagent formation, but at the same time they promote the initiation of the reaction.

3.3. Inhibition in Toluene

We extended this study to the toluene medium in connection with our interest in preparation of a Grignard reagent in toluene in the presence of small additions of organic bases[20-22]. It was also caused by insufficient solubility of a potential inhibitor, anthracene, in diethyl ether. The inhibitory action of water can, of course, be investigated but it involves great difficulties because of its low solubility in toluene.

The Grignard reaction in toluene can be accomplished in presence of catalytic amounts of diethyl ether[21]. In binary mixtures of the latter with toluene the course of the Grignard reaction varies very little up to comparable molar concentration of ether and organic halide[20]. When the additions of ether are less than two moles to a mole of halide, a distinct dependence of the reaction rate on the relative content of ether can be observed[20,21]. n-Butyl magnesium bromide solvated by ether is well soluble in toluene[22].

We investigated the inhibitory activity of several alcohols and anthracene in toluene at equimolar ratio of diethyl ether to n-butyl bromide, and that of methanol and n-butyl alcohol at a molar ratio 0.5 : 1 of ether to halide. The results of the measurements are presented in Table 4 and the dependence of apparent initiation constants on the initial concentration of the inhibitor are presented in Fig. 5.

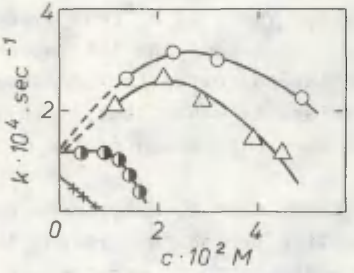

Fig. 5. Dependence of the apparent initiation constant on initial concentration of inhibitors in toluene: ○ - n-butanol, △ - n-octanol, ◑ - methanol,(ratio of diethyl ether to n-butyl bromide 1:1), + - methanol (ratio of diethyl ether to n-butyl bromide 0.5:1).

In toluene n-butyl and n-octyl alcohols reveal the dependence of the initiation constant on additions of the in-

hibitor with a maximum. Methanol also produces a curve, different from the one obtained in pure ether (cf. Fig.3). In our opinion, in toluene more distinctly than in ether the dualistic effect of alcohols on the induction period becomes evident. On the one hand, they act as inhibitors, but on the other hand, complexing with the products, alcohols promote solution of the oxidic film of magnesium. Obviously, the solubility of such complexes in toluene is poorer than in ether, except, possibly, that of methanol. They set to deposit on the surface of magnesium and therefore, within the range of used additions of alcohols, one can observe a maximum and further decrease in the value of the apparent initiation constant. As in the case of ether, (section 3.2), all curves intersect in a common point k_o^*. The value of the intrinsic initiation constant, k_o^*, is about $1.2 \cdot 10^{-4}$ sec^{-1} (ether concentration 0.86 M), which is more than four times greater than that for pure ether (about $5.2 \cdot 10^{-4}$ sec^{-1} at 9.5 M ether). When the molar ratio of ether to halide was 0.5:1 (concentration of ether about 0.4 M), the value of k_o^* was even less, about $0.6 \cdot 10^{-4}$ sec^{-1}. It follows that the initiation constant strongly depends on the concentration of ether in the reaction mixture. Otherwise, it means that diethyl ether directly participates in the initiation of the Grignard reaction.

As it is seen from Table 4, anthracene exerted no influence on the induction period. Anthracene is known as a good trap for free radicals[23]. It was frequently used for detection of free alkyl and aryl radicals in reaction mixture[24, 25]. A total lack of the inhibitory action of anthracene in this experiment indicates that free radicals are not the essential intermediates during the induction period, and inhibition does not consist in capturing free radicals.

Table 4

Induction Periods and Initiation Constants in Toluene

CH_3OH [a]			$n\text{-}C_4H_9OH$ [a]			$n\text{-}C_8H_{17}OH$ [a]		
$c \cdot 10^2$ [c]	t [d]	$k \cdot 10^4$ [e]	$c \cdot 10^2$ [c]	t [d]	$k \cdot 10^4$ [e]	$c \cdot 10^2$ [c]	t [d]	$k \cdot 10^4$ [e]
0	120	-	0	125	-	0	111	-
0.45	163	1.20	1.35	184	2.65	1.14	173	2.10
0.91	210	1.17	2.30	209	3.18	2.13	204	2.66
1.20	252	1.05	3.20	248	3.02	2.90	258	2.29
1.40	353	0.70	4.88	375	2.26	3.89	419	1.47
1.60	609	0.38				4.50	562	1.16

anthracene [a]		CH_3OH [b]		$n\text{-}C_4H_9OH$ [b]	
$c \cdot 10^2$ [c]	t [d]	$c \cdot 10^2$ [c]	$k \cdot 10^4$ [e]	$c \cdot 10^2$ [c]	$k \cdot 10^4$ [e]
0	115	0	-	0	-
0.60	113	0.27	0.47	0.54	1.30
1.00	117	0.49	0.31	0.94	1.79
1.50	118	0.74	0.19	1.66	2.78
2.45	117				

a) ethyl ether : n-butyl bromide = 1:1
b) ethyl ether: n-butyl bromide = 0.5:1
c) initial concentration of the inhibitor, mole/l
d) induction period, sec.
e) initiation constant, sec^{-1}.

4. Nature of Induction Period.

In the previous section, it was concluded proceeding from the absence of the inhibitory action of anthracene that the inhibition of the Grignard reaction does not consist in trapping of free radicals. The same can be inferred from the fact that iodine was not consumed during the induction period but it only disappeared after vigorous formation of the Grignard reagent had begun. It is to be mentioned that iodine was present in molar quantities, which was 3-60 times less than that of added inhibitors.

In general, the formation of a Grignard reagent is believed to be a free-radical process. Therefore it would be reasonable to assume that inhibition lies in a reaction with free radicals. However, the classical inhibitor - water, cannot serve as a trap for alkyl or aryl radicals. In water, alcohols interacted with free radicals through methylenic hydrogen atoms instead of the hydroxylic ones[26,27]. This is not compatible with principally similar behaviors of water, methanol, and alcohols containing a methylenic group in the sense that the data for all inhibitors without any exceptions, by our treatment yielded the same k_o^{M} value. Indeed, a reaction of a free radical with an alcohol generates another radical which can attack an ether molecule giving rise to a radical chain that may exert a certain inhibition effect. Therefore, it is improbable that factor f in the expression for k_o would have a unit value for all the inhibitors used

$$k_o = \frac{f[\text{Inh}]_o}{t_i [\text{A}]_o}$$

In the opposite case, the dependence of the apparent initiation constant on the initial molar concentration of the inhibitor (Fig. 3) would lead to different values of constant k_o^{M} for different inhibitors. Taking into account all the above-mentioned statements and the fact that water inhibits only with one equivalents of hydrogen[A], we can conclude that during the induction period the inhibitors react with the Grignard reagent steadily entering the solution.

Our conclusion is consistent with the finding of Walborsky et al.[28] that methanol, added to the Grignard reaction mixture behaved like an OH-acid and not like a substrate of a free-radical attack. Thus, our results might be used as objections in the discussion about the problem whether the free radicals formed in the Grignard reaction can freely enter the solution (refs. [29], [30], on the other hand[28], see also[9], [14]). However, it is to be taken into account that in this case the process is probably complicated by diffusion through the pores in the oxidic film. Therefore, the results can hardly be indisputably transferred to a system with a bare surface of magnesium metal. Nevertheless, it is clear now that the decisive point of the induction period is the cleansing of magnesium surface from the oxidic film. Gilman[2] already noticed the inhibitory effect of oxygen. Investigation of anodic solution of magnesium in dimethylformamide and other solvents has shown that oxygen causes a serious retardation of the process[31]. The influence of water appeared to be considerably weaker, becoming perceptible only at the concentrations above 0.1% by volume.

Apparently, the commencement of the Grignard reaction can proceed as follows. The organic halide and ether diffuse through the pores in the oxidic film to the surface of magnesium. Access to the magnesium surface is also available through the spots of mechanical damage caused by vigorous stirring of the reaction mixture. The forming Grignard reagent dissolves oxide, gradually baring the metal surface. The reaction is accelerated autocatalytically and when the surface is completely uncovered, the reaction rate will be equal to that observed at the end of the induction period. Inhibitors react with the Grignard reagent retarding thereby the cleansing process of magnesium surface. At that poorly soluble products can form. The latter can deposit on the surface of magnesium metal together with magnesium oxide liberated from decomposed complexes. At the beginning of the process the precipitate can stop up the pores in the oxidic film. Therefore, a certain cri-

tical addition of the inhibitor can totally suppress the reaction. Some inhibitors, e.g. higher alcohols, lead to soluble products which can to a certain extent dissolve magnesium oxide. In such cases the dependence of the apparent initiation constant on the initial concentration of the inhibitor exhibits either a positive slope (Fig. 4) or a maximum.(Fig. 5).

5. Experimental Part

Reagents and Solvents

Diethyl ether was treated with potassium hydroxide, dried over calcium chloride and distilled over sodium wire.

Toluene was washed with conc. sulfuric acid, dried over calcium chloride and distilled over sodium wire.

n-Butyl bromide was dried over calcium chloride and fractionated before use.

Magnesium metal, commercial grade, was used in the form of chippings.

Water for inhibition was twice distilled, deuterium oxide (D_2O), TU 95.7046-73, isotopic purity 99.9% was also distilled. Methanol and ethanol were dried with metallic magnesium and fractionated. n-Buthanol and n-octanol were fractionated before use. Stearic acid and anthracene were of "pure for analysis" grade.

Preparation of Solutions

The solvents were distilled into previously weighed flasks and their amounts were determined by weighing. Inhibitors were weighed in a weighing tube which was thereupon immersed in the flask with the solvent. The procedure was repeated with iodine. Solutions for measurements were prepared in flasks, the required amounts of n-butyl bromide and solutions of inhibitors and iodine were transported by means of calibrated hypodermic syringes.

Determination of the Induction Period

Into a test-tube whose diameter was 30 mm and which was capped with a glass stopper was placed 0.3 g of magnesium shavings and a magnetic stirring bar. By means of a calibrated hypodermic syringe 10.0±0.1 ml of reaction solution were introduced, then stirring and time measurements started. Disappearance of the coloring of iodine visible against white background with good lightening was considered the end of the induction period. The measurements were carried out at 20±1° C. The duration of the induction period was determined as the mean value of 3-5 measurements. Reproducibility of determinations was ±5 sec on the average, in case of long induction periods, the deviations were greater but they did not exceed ±15 sec.

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INFLUENCE OF SONICATION ON THE INDUCTION PERIOD OF THE GRIGNARD REACTION

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The induction period of the reaction of n-butyl bromide with metallic magnesium in diethyl ether and in toluene with an addition of diethyl ether was investigated under ultrasonic irradiation in presence of the following inhibitors: water, methanol, ethanol, 1-butanol, 1-octanol, and stearic acid. In the presence of ultrasonication the reaction can be easily initiated. The effect of ultrasound mainly consists in destruction of the oxidic film of magnesium. It also prevents the deposition of reaction products on the surface of magnesium.

Under ordinary conditions the reaction between metallic magnesium and organic halide does not start immediately but only after an induction period. The duration of the induction period may greatly vary owing to the action of different activators and inhibitors[1]. We have shown[2] that the Grignard reagent, formed within the induction period, dissolves magnesium oxide gradually uncovering the surface of magnesium metal. At the same time slightly soluble products may form that deposit on the surface of the metal. At the beginning of the process they can stop up the pores in the

oxidic film. That is why the reaction is totally suppressed by a critical addition of the inhibitor. Several inhibitors (e.g., higher alcohols) lead to soluble products that can to some extent dissolve magnesium oxide and thus promote the initiation. Sometimes the induction period may last hours, therefore a reduction of the latter would be of practical interest. Various ways of shortening or averting the induction period (reviews in refs. [1,2]) have been proposed, including the ultrasonic irradiation. It has been found that ultrasound is able to initiate the Grignard reaction in the presence of such amounts of water or ethanol that make the reaction impossible in ordinary conditions[3,4]. A considerable shortening of the induction period has been observed in ultrasonic conditions[4-7] besides the ethereal solutions also in mixtures of diethyl ether with unsolvated solvents[4,7]. In all cases investigated the use of ultrasound did not practically affect the yield of Grignard reagent[3-7].

We studied[7] the kinetics of the Grignard reagent formation both in the field of ultrasound and without sonication. The accelerating effect of sonication was found, however, general kinetic nature of the reaction did not change. Systematic quantitative investigations of the effect of ultrasonic irradiation on the induction period of the Grignard reaction have not been conducted up to now yet.

We extended our investigation of the action of inhibitors on the induction period of the Grignard reaction[2] to the field of sonochemistry in order to obtain some confirmation of our preliminary conclusions about the nature of the induction period. Our another aim was a more detailed study of the influence of ultrasonication upon the induction period of the reaction. Like in the previous work[2], the reaction of n-butyl bromide with magnesium metal in diethyl ether and in toluene with an addition of diethyl ether was investigated. In principal, the same method[2] of determination of induction period was used, based on the fact that the color of a small admixture of iodine rapidly

disappeared by the end of the induction period. Similarly to the previous work we ascertained that iodine did not react with magnesium, n-butyl bromide, and solvents within a sonication time exceeding that used in this work. Induction period was determined both in absence and in the presence of additions of various inhibitors. From these data were calculated the apparent initiation constants k_0 (see reference[2] and the experimental part of this work). In the previous work we found that the dependence of the latter on the initial concentration of the inhibitor, as well as the intrinsic constant of initiation, k_0^{∞}, obtained by extrapolation of this dependence to zero addition of the inhibitor, offer valuable information about the nature of the induction period and about the participation of inhibitors in the latter.

Experimental

Preparation of Solutions.

Reagents, solvents and inhibitors were purified as described earlier[2]. The solvents were distilled into previously weighed flasks and their amount was determined by weighing. Inhibitors were weighed in a weighing tube which was thereupon sunk in the flask with the solvent. The same was done with iodine. Solutions for measurements were prepared in flasks, required amounts of n-butyl bromide and of solutions of inhibitors and iodine were transported by means of calibrated hypodermic syringes.

Apparatus.

The reaction was carried out in a tightly closed test-tube of 30 mm diameter. As a source of ultrasound, a dispersor UZDN-2T was employed. Its conic ultrasound probe was immersed into the reaction mixture through the plug of the test tube. The probe made of titanium had on its end a round tip with a diameter of 15 mm. The device operated at 22 kHz, its nominal electrical energy output was 400 W. The acoustical capacity of an analogous system was deter-

mined in our recent work[7]. A rough estimation for this system is as high as 10 W/cm^3.

Determination of the Induction Period.

The test-tube was loaded with 0.3 g of magnesium metal and joined to the ultrasound device. Through an opening in the stopper 10 ± 0.1 ml of reaction solution were introduced by means of a calibrated hypodermic syringe and both the ultrasonic irradiation and the clock were switched on. The moment of disappearance of the coloring of iodine visible against white background with good lighting was taken as the end of induction period. The duration of induction period was determined as a mean value of 4-5 measurements. The reproducibility of determination was ±7 sec on average.

The initial temperature of the apparatus and of the solutions was $20\pm1^{\circ}$ C. However, the sonication evokes a rapid warming up of the reaction mixture. Therefore, immediately after the beginning of sonication, the reaction vessel was immersed into ice water. In spite of that the temperature of the reaction mixture rose in a few minutes by 10° or more. Because of the latter we confined ourselves to short induction periods (less than 2 min.), the rise in the temperature was no more than a few degrees there.

Initial concentrations of the reagents were for n-butyl bromide 0.86 M, iodine 0.001 M, and inhibitors from 0.006 M to 0.075 M.

Calculation of the Apparent Initiation Constant.

Apparent initiation constants, k_o, for various additions of inhibitors were calculated by formula (see ref.[2]):

$$k_o = \frac{[\mathrm{Inh}]_o}{(t_i - t_i^o)[\mathrm{A}]_o},$$

where $[\mathrm{Inh}]_o$ and $[\mathrm{A}]_o$ are the initial concentrations of the inhibitor, and n-butyl bromide, respectively, and t_i and t_i^o denote the induction period for the present addition of the inhibitor, and without any inhibitor, respectively.

Results and Discussion

Influence of Temperature on Initiation

The difficulties in temperature control in the reaction mixture by sonication (see Experimental) led us to estimate the activation energy of initiation. Using a technique described in the previous paper[2], we determined apparent initiation constants for several additions of inhibitors at 15° and 32° C. The results of determination and the calculated energies of activation are presented in Table 1.

On the average, the found activation energies are about 9-10 kcal/mole, thus coinciding with an estimation of about 10 kcal/mole from the data published by Gilman[8]

Table 1

Dependence of the Initiation Constant on the Temperature (without Sonication)

Admixture	H_2O		CH_3OH		$n\text{-}C_4H_9OH$	
$c \cdot 10^2$ M	1.36		1.09		2.60	
t° C	15	32	15	32	15	32
$k_o \cdot 10^4$ s^{-1}	1.73	5.11	1.06	2.26	4.0	9.7
E_a kcal/mol	11.3		7.8		9.2	

for the induction period of n-butyl bromide in pure ether at 17° and 26° C. It is of some interest to mention that obviously this is a higher value than that for an ordinary Grignard reaction. There is very little information about the latter, however, for the reaction of cyclohexyl bromide with magnesium the activation energy was estimated[9] to be about 2.3 kcal/mol. It follows that in general the temperature dependence of the initiation constant must not be ignored. Considering the data of this work, one has to

consider that the apparent initiation constants obtained from a long induction period are somewhat magnified, however, this does not change the general trend of the dependences under consideration.

Inhibition in Diethyl Ether.

Induction periods and the corresponding calculated initiation constants for various additions of inhibitors are presented in Table 2. The dependence of apparent initiation constants on the initial concentration of the inhibitor is represented in Fig. 1.

Table 2

Induction Period and Initiation Constants in Diethyl Ether

$c \cdot 10^2$	t	$k_o \cdot 10^3$	$c \cdot 10^2$	t	$k_o \cdot 10^3$	$c \cdot 10^2$	t	$k_o \cdot 10^3$
	H_2O			C_2H_5OH			$n\text{-}C_8H_{17}OH$	
0	15	-	0	13	-	0	12	-
0.65	21	1.26	1.15	21	1.68	1.19	20	1.73
1.22	26	1.29	2.30	29	1.67	2.40	25	2.10
1.86	39	0.90	3.60	33	2.08	3.76	32	2.20
2.48	48	0.87	4.60	49	1.51	6.90	68	1.40
2.95	65	0.68		$n\text{-}C_4H_9OH$			$n\text{-}C_{17}H_{35}COOH$	
3.66	74	0.72						
4.35	102	0.58	0	15	-	0	14	-
	CH_3OH		2.02	26	2.14	1.75	26	1.70
			4.08	41	1.80	4.00	36	2.10
0	12	-	5.60	53	1.70	7.50	96	1.06
1.10	26	0.90						
2.07	45	0.72						
3.20	71	0.62						
4.44	112	0.52						

c - initial concentration of the inhibitor, $mole \cdot l^{-1}$

t - induction period, sec

k_o - initiation constant, sec^{-1}

In spite of a rather great scatter of points, it can be seen that water and methanol give downword dependences but other inhibitors form an upword curve with a maximum. In general, this feature coincides with that revealed for the case when there is no sonication[2], except ethanol, which under sonication resembles rather the inhibitors promoting the initiation. Probably, a relative significance of the solubility of ethoxide complexes, of their capability to adhere to the metal surface, and of dispersive power of the sonication is such that the behavior of ethanol differs from that of water and methanol.

Under sonication, even in the case of great admixtures of inhibitors the initiation constants have such values that the Grignard reaction can quite easily be accomplished in diethyl ether saturated by water ($4.6 \cdot 10^{-2}$M) or in the presence of considerable admixtures of alcohols, as it was also noticed earlier[3,4,5].

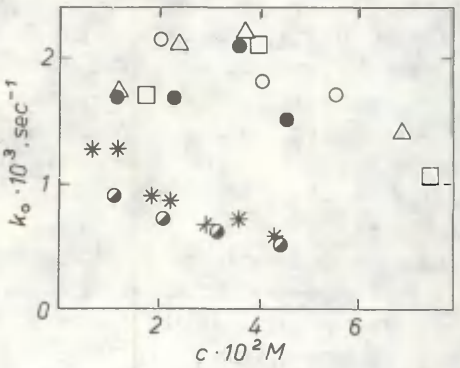

Fig. 1. Dependence of apparent initiation constant on initial concentration of inhibitors in diethyl ether: ✱ - water; ◪ - methanol; ● - ethanol; ○ - 1-butanol; △ - 1-octanol; □ - stearic acid.

From Fig. 1 we can estimate a value for the intrinsic initiation constant to be about $1.5 \cdot 10^{-3} sec^{-1}$. The latter is nearly three times higher than that obtained in absence of ultrasonication. The promoting effect of sonication on the initiation process has also been proved by a reduction of the induction period without inhibitors from 56-72 sec in absence of sonication[2] to 12-15 sec in the presence of the latter. Evidently, ultrasonic irradiation does not only accelerate diffusion but it also causes a partial destruction of the oxidic cover of magnesium. The latter conclusion is supported by an increase in the rate of an ordinary Grignard reaction under sonication only by a factor of two[7].

Inhibition in Toluene.

The Grignard reaction can be carried out in toluene in the presence of catalytic amounts of diethyl ether, even less than one mole to a mole of organic halide[10]. n-butylmagnesium solvated by ether is easily soluble in toluene[11].

In absence of sonication[2], replacement of diethyl ether by toluene (with a remainder equimolar ratio of ether to n-butyl bromide) causes difficulties in the initiation. The value of intrinsic initiation constant, $k_o^{\ni}$, decreases by a factor exceeding four, and the dependence of the apparent initiation constant on the initial concentration of the inhibitor reaches its maximum in the region of small additions of the inhibitor.

As can be seen from Table 3 and Fig. 2, in case of sonication, the replacement of ether by toluene does not suppress the initiation but, on the contrary, it slightly accelerates the process. Duration of the induction period in absence of added inhibitors shortens, the values for apparent and intrinsic initiation constants are higher than in the case of diethyl ether. In our opinion, this may be associated with a lower vapor tension of toluene in comparison with diethyl ether, making the cavitation phenomena in toluene more substantial[12]. The latter, in its turn, confirms the decisive role of destruction of the oxidic film of magnesium in the induction period.

Table 3

Induction Period and Initiation Constants in Toluene[a]

CH_3OH			$n\text{-}C_4H_9OH$		
$c \cdot 10^2$	t	$k_o \cdot 10^3$	$c \cdot 10^2$	t	$k_o \cdot 10^3$
0	10	-	0	9	-
0.98	18	1.42	1.30	16	2.15
1.80	26	1.31	2.50	21	2.40
3.10	38	1.28	3.80	25	2.76
4.50	63	0.98			

a) equimolar ratio of diethyl ether and n-butyl bromide;
c - initial concentration of the inhibitor, $mole \cdot l^{-1}$;
t - induction period, sec.
k_o - initiation constant, sec^{-1}.

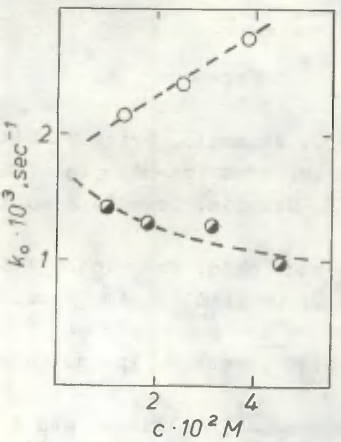

Fig. 2. Dependence of apparent initiation constant on initial concentration of inhibitors in toluene:
◒ - methanol, ○ - 1-butanol.

Conclusions

We found that ultrasonication facilitates the initiation of the Grignard reaction. Induction period shortens, the initiation constants acquire higher values and the reaction starts in the presence of such admixtures of inhibitors which totally suppress the reaction in absence of ultrasonication.

The patterns of the influence of inhibitors on the induction period do not generally change under sonication, except a particular difference that the replacement of diethyl with toluene reinforces sonication effect. The latter fact together with the information obtained in this work is in good accordance with our assumption that the induction period of the Grignard reaction is mainly conditioned by the necessity of cleansing magnesium surface by the Grignard reagent formed in the reaction. Ultrasonic irradiation facilitates the destruction of the oxidic film and counteracts deposition of reaction products on the surface of magnesium.

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THE ACIDITY OF SOME NEUTRAL AND CATIONIC ORGANIC ACIDS IN 7.75 MOLAL AQUEOUS SOLUTION OF TETRABUTYLAMMONIUM BROMIDE

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Potentiometric titration was used for determination of the pK_a values for dissociation of several aliphatic and aromatic carboxylic acids, phenols and substituted ammonium ions in 7.75 molal (2.34M) aqueous solution of $(C_4H_9)_4NBr$ (Bu_4NBr).

The present results and those of Steigman and Sussman on the pK_{as} values of acidic dissociation of various organic acids in the above mentioned aqueous solution of Bu_4NBr were compared with the corresponding pK_a values for the aqueous solution (without Bu_4NBr).

It was shown that for the various reaction series the following linear relationship

$$pK_{as}^{i} = b_i pK_a^{i} + a_i \ , \qquad (1)$$

where pK_{as} and pK_a refer to the i-th reaction series

and b_i and a_i depend on the nature of the latter and on the solvent.

holds between the pK_{as} and pK_a values.

Earlier it was shown that the electrophilic solvating power of aqueous solutions of Bu_4NBr decreases very significantly with the increase in the concentration of this salt. Namely, it was found[1] that the solvent gross polarity parameter E_T for the highly concentrated (cá 3M or ≈30 molal) aqueous solutions of Bu_4NBr almost reaches the values which are characteristic of the dipolar aprotic solvent, DMSO, or of the pure liquid quarternary salt, $C_6H_5COO[(C_5H_{11})_4N)]$.

It is known that, as a rule, but far from being always so, the variation of the solvent's solvation characteristics[2] induces rather significant changes in the pK_a values of the acid-base equilibria (see Refs. 3-10 and those given therein). Therefore, one can also expect that in some cases the transfer of various reaction series (dissociation of aliphatic and aromatic carboxylic acids, ammonium ions, etc.) of that type from pure water into the more concentrated aqueous solutions of Bu_4NBr could be accompanied not only by the changes in the absolute pK_a values for different acids or bases but also by a significant variation of the relative sensitivity of those reaction series towards substituent effects.

The above-said is also in accordance with the results of Steigman and Sussman[11,12] who have determined the pK_a values for the acidic dissociation of substituted benzoic acids, phenols, anilinium ions as well as for several aliphatic carboxylic acids and ammonium ions in 7.75 molal (2.34M) aqueous solution of Bu_4NBr.

According to its characteristics of gross-polarity (E_T = 49.6 kcal/mol) and electrophilicity (E = 9.3), 7.75 molal aqueous solution of Bu_4NBr is[1] somewhat closer to water (E_T = 63.3 kcal/mol, E = 21.7) than to the DMSO (E_T = = 45.0 kcal/mol, E = 3.3) or ≈30 molal aqueous solution of Bu_4NBr (E_T = 46.4 kcal/mol, E = 7.6). Therefore, one can expect that the pK_a values measured for the various reaction series in the 7.75 molal aqueous solution of Bu_4NBr

should range somewhere in between the corresponding pK_a values for water, on the one hand, and for DMSO or 30 molal aqueous solution of Bu_4NBr, on the other hand.

Indeed, the analysis of the data of the above mentioned authors[11,12] shows that, as compared with water, the measured pK_a values for the neutral OH-acids in 7.75 molal solution of Bu_4NBr increase significantly (cá by 2 pK_a units) whereas in the case of reaction series of acidic dissociation of aliphatic ammonium ions, in accordance with the results from other sources[3,7,13] the absolute pK_a values remain almost unchanged.

A thorough comparative analysis of solvent effects on the relative sensitivity of various acid-base equilibria towards structural effects accompanying the transfer from water into 7.75 molal aqueous solution of Bu_4NBr, was performed[14] in 1978 in terms of Eq. (1). An inference was made that on the basis of the existing by that time data, Eq. (1) holds for all reaction series considered. It was suggested that while the slopes b_i for various reaction series are, as a rule, different, the intercepts a_i for separate straight lines coincide with each other within their statistical reliability limits. In the other words, it was accepted that in the terms of Eq. (1) the points for various groups of the reaction series concentrate around different straight lines, characterized by different slopes b_i but having one and the only crossing point (probably, somewhat unexpectedly, vide infra), i.e., the common intercept.

Indeed, in the simplest case one can assume that the pK^i_{as} and pK^i_{ak} values for the i-th process in solvents s and k depend only on one and the same internal structural factor (e.g., inductive effect or the electronegativity of the substituent , effective charge on the reaction center, etc.) which is quantitatively characterized by some X_i parameters (e.g., σ^*, σ^o, etc. substituent constants, etc.).

In the case of linear relationships between pK^i_{as} and pK^i_{ak} values and X_i- parameters one can write:

$$pK^i_{as} = a_{os} + b_s X_i \qquad (2)$$

and

$$pK_{ak}^{i} = a_{ok} + b_k X_i \ , \qquad (3)$$

where a_{os} and a_{ok} are the pK_a values for the reference substituent with $X_i = 0$ and b_s and b_k are the characteristics of the corresponding reaction series.

Combining of Eqs. (2) and (3) leads to the relationship which is identical to Eq. (1):

$$pK_{as}^{i} = b_i pK_{ak}^{i} + a_i \ , \qquad (4)$$

where $b_i = b_s/b_k$ (5)

and

$$a_i = a_{os} - a_{ok}(b_s/b_k) \qquad (6)$$

Evidently, relationships analogous to Eqs. (2)-(6) can probably be written also for any other arbitrarily chosen j-th, l-th, etc. processes. Hence, even in the simplest case (pK_a values are assumed to depend only on one structural factor), the necessary condition for the common intercept for the straight lines for the comparison of pK_a values for different reaction series i, j, l, etc. (e.g., aliphatic and aromatic acids, etc.) in two solvents s and k would be a rather unlikely independence (constancy) of quantities $a_i = a_{os} - a_{ok}(b_s/b_k)$ of the nature of the reaction series.

Due to somewhat scarce data[11,12] (only a limited number of measurements of pK_a in aqueous Bu_4NBr solution for aliphatic and aromatic ammonium ions and substituted phenols) which were available to the author of Ref. 14 in the present work an attempt was made towards a further verification of Eqs. (1) and (4) on the basis of more extensive and statistically more representative data set of the pK_a values for the 7.75 molal aqueous solution of Bu_4NBr. To meet this goal in the present work the pK_{as} values for several neutral and cationic acids were measured in 7.75 molal aqueous Bu_4NBr solution, hereby in a way extending the covered pK_a range and the choice of substituents.

Experimental

The potentiometric technique of Steigman and Sussman[11,12] was adopted in its major features for the determination of pK_a values for some neutral and cationic acids in 7.75 molal aqueous solution of Bu_4NBr. The aqueous 1 M solution of KOH was used as a titrant.

The titration equipment originally designed for the determination[5,7,8,15] of pK_a values of various neutral and cationic acids in DMSO solution was used.

Bu_4NBr ("pure") was purified as described in Ref.[1].

The measured pK_a values of acids in 7.75 molal aqueous Bu_4Br were standardized relative to the pK_{as} value for the benzoic acid which was used (pK_{as} = 6.30) by Steigman and Sussman[11,12]. The reproducibility of the measured pK_a values was in the range of ± 0.05 $\div$ 0.1 units of pK_a.

The pK_a values for 7.75 molal aqueous solution of Bu_4NBr measured in this work are given in Table 1.

The statistical analysis of the present data in terms of Eqs. (1) and (4) and those of Steigman and Sussman[11,12] for the 7.75 molal aqueous solution of Bu_4NBr, on the one hand, and the corresponding pK_a values for the aqueous solution[14,16], on the other hand, was performed separately for various reaction series using the method of the least squares. The results of such an analysis are given in Table 2 and visualized in Fig. 1.

Discussion

One can see from Table 2 and Fig. 1 that in some approximation the transfer of various reaction series for the acidic dissociation of neutral and cationic Brønsted acids could be characterized in terms of Eq. (1) or Eq. (4). At the same time there is no doubt that in some cases the slopes b_i as well as intercepts a_1 of the resulting straight lines could vary rather significantly. So, for

Table 1

pK_a Values for Some Neutral and Cationic Acids in 7.75 Molal Aqueous Solution of Bu_4NBr at 25° C[a]

	Acid	pK_a
1.	C_6H_5COOH	6.30[11,12]
2.	$C_6H_5CH_2COOH$	6.60±0.10
3.	$CNCH_2COOH$	3.95±0.04
4.	$F_2CHCOOH$	2.91±0.10
5.	CF_3COOH	1.85±0.04
6.	$HC{\equiv}CCOOH$	4.10±0.07
7.	$(CH_3)_3CCOOH$	7.26±0.04
8.	$3\text{-}CF_3C_6H_4COOH$	5.40±0.05
9.	$3,5\text{-}(CF_3)_2C_6H_3COOH$	4.08±0.05
10.	$2,6\text{-}(NO_2)_2C_6H_3OH$	3.30±0.15
11.	$(CH_3)_3N(Cl)CH_2COOH$	3.14±0.03
12.	$2,4,6\text{-}(NO_2)_3C_6H_2OH$	1.95±0.10
13.	$CH_3ONH_2\cdot HCl$	4.77±0.05
14.	$CH_3ONHCH_3\cdot HCl$	6.70±0.10
15.	$(CH_3)_2NOH\cdot HCl$	5.85±0.05
16.	$(CH_3)_2NCH_2CN\cdot HClO_4$	4.17±0.06
17.	$CF_3CH_2NH_2\cdot HCl$	5.45±0.10
18.	$(CH_3)_2NCH_2COOC_2H_5\cdot HClO_4$	6.83±0.10

a - The error limits for the pK_a values are indicated. The concentrations of the acids titrated were in the range of 5×10^{-3} ~~+~~ 3×10^{-2} mole/liter.

Table 2

The Results of the Statistical Analysis of Comparison in Terms of Eqs. (1) and (4) of the Acidity of Some Neutral and Cationic Acids in 7.75 Molal Aqueous Solution of Bu_4NBr and Water*

Reaction series	b	a_i	r	s	n
1	2	3	4	5	6
1. a) Aliphatic XCOOH	1.30 (0.05)	0.72 (0.23)	0.973	0.49	37
b) -"-	1.18 (0.02)	1.29 (0.11)	0.994	0.18	29**
2. Benzoic Acids					
a) 2-X-C_6H_4COOH	0.967 (0.096)	2.82 (0.31)	0.971	0.16	8
b) 3-X-C_6H_4COOH	2.08 (0.20)	-2.36 (0.78)	0.961	0.14	11
c) 4-X-C_6H_4COOH	1.95 (0.19)	-2.04 (0.78)	0.960	0.22	11
3. Phenols					
a) 2,6-X_1X_2-C_6H_3OH	1.49 (0.06)	-2.71 (0.42)	0.999	0.23	3
b) 3-X-C_6H_4OH	1.35	-1.36	-	-	2

Table 2 continued

1	2	3	4	5	6
c) 4-X-C_6H_4OH	1.45	-2.1	-	-	2
d) 2-,3-, and 4-substituted phenols	1.46 (0.04)	-2.39 (0.29)	0.998	0.23	7***
4. Aliphatic ammonium ions					
a) XNH_3^+	0.957 (0.016)	0.37 (0.16)	0.999	0.09	13
b) $X_1X_2NH_2^+$	0.613 (0.061)	3.71 (0.63)	0.963	0.36	10
c) $X_1X_2X_3NH^+$	0.726 (0.108)	2.09 (0.88)	0.959	0.74	6

x In the 2nd and 3rd columns of the Table in the parentheses under regression coefficients a_i and b_i are indicated their reliability intervals, r and s are respectively, the correlation coefficient and standard deviation, n - the number of points.

** The points for X=CH_2COOH, $(CH_2)_2COOH$, $C(CH_3)_2COOH$, $C(CH_3)_2COO^-$, $C(n\text{-}C_3H_7)_2COOH$, $O(n\text{-}C_3H_7)_2COO^-$, cis-CH=CHOOOH, and C≡CH were excluded

*** The point for the picric acid was excluded.

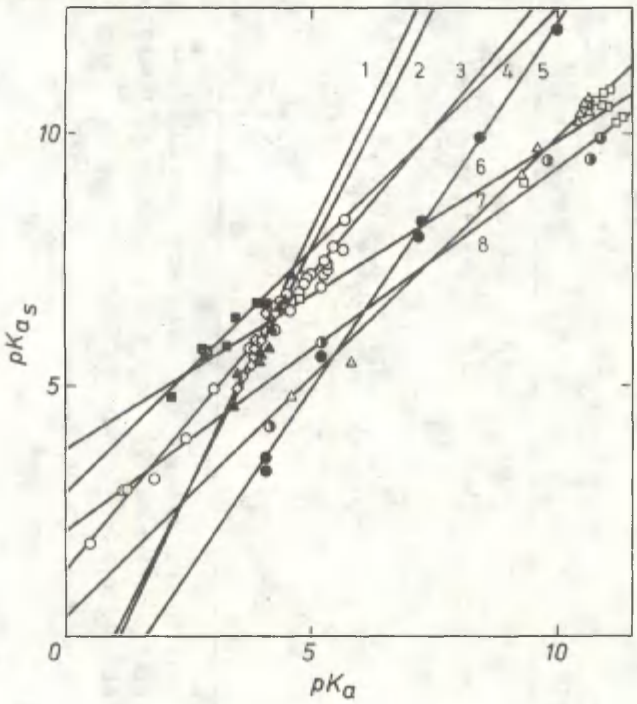

Fig. 1. Comparison of acidities of some neutral and cationic acids in 7.75 molal aqueous solution of Bu_4NBr (pK_{as}) and water (pK_a): 1) 3-substituted benzoic acids (◇), 2)4-substituted benzoic acids (▲), 3) aliphatic carboxylic acids (○) (series 1b from Table 2), 4) 2-substituted benzoic acids (■), 5) 2-,3-, or 4-substituted phenols (●), 6) secondary ammonium ions (□), 7) primary ammonium ions (△) 8) tertiary ammonium ions (◑).

two reaction series (primary ammonium ions and 2-substituted benzoic acids) the sensitivities of the latter towards the substituent effects in the 7.75 molal aqueous solution of Bu_4NBr and in pure water are practically identical within their reliability intervals. An analogous transfer of aliphatic carboxylic acids, substituted phenols and 3- or 4-substituted benzoic acids from water into salt solutions results in an unquestionable increase in these reaction series towards structural factors due to a decrease[1] in the electrophilicity of the solvent. At the same time, unlike the reaction series of 2-, 3-, and 4-substituted benzoic acids, the available rather scarce data for the 2-, 3-, and 4-substituted phenols evidence in favor of the approximately similar sensitivity towards substituent effects in case of the latter reaction series in water and in the 7.75 aqueous solution of Bu_4NBr.

In the case of two reaction series, i.e., acidic dissociation of secondary and tertiary aliphatic ammonium ions the b_i value in 7.75 molal salt solution is somewhat lower than the corresponding value for aqueous solution. This situation is similar to the findings described in Ref. 7 regarding the transfer of the reactions of the acidic dissociation of aliphatic ammonium ions from dipolar aprotic solvent DMSO into water.

It also follows from Table 2 and literature [3,5,7,8] that the sensitivities of the reaction series of the acidic dissociation of OH-acids towards substituent effects in the 7.75 molal aqueous solution of Bu_4NBr are closer to the corresponding values for pure water than to the values that refer to the DMSO solution. As already suggested in the present paper (vide supra), this statement seems to result from the fact that the electrophilicity (this solvent property is primarily[3,5,17] responsible for the stabilization of the anionic form of OH-acids) of the 7.75 molal aqueous Bu_4NBr solution is closer to the electrophilicity of water than that of DMSO.*

* The mechanism of the influence of solvent-solute interactions on the relative reactivity towards solvent effects

It follows from the above-said (see Eq. (6)) that in an hypothetical simple case (the influence of only one structural factor on the given i-th reaction series in two solvents, s and k) intercept a_i from Eqs. (1) and (4) is determined by the difference of the absolute pK_a values for reference compounds in solvents a and k, which is corrected for the ratio b_s/b_k of the sensitivities of the i-th reaction series towards the involved structural factor in those two solvents.

It is evident that in this case only on condition that $b_s/b_k = 1$, intercept a_i from Eqs. (1) and (4) is equal to the difference between a_{os} and a_{ok} (see Eqs. (2) and (3)). According to the results of the statistical analysis of the experimental data in terms of Eq. (1) (see Table 2) this condition seems to be fulfilled for the reaction series of dissociation of the primary aliphatic ammonium ions whose a_i value is practically indistinguishable from zero (see Table 2, series 4a), whereas slope b_i is close to unity. These circumstances seem to evidence the overall compensation for the influence of various non-specific and specific solvent-solute interactions[2] which govern the transfer of the neutral primary amine into its protonated form while going from water into the 7.75 molal aqueous solution of Bu_4NBr.

Equations (2)-(6) were written for the given i-th reaction series, whereas the only operating mechanism for the substituent effect was assumed. It is not surprising that in case of statistical data processing in terms of Eq. (1) for comparison of various reaction series of different chemical nature (aliphatic and aromatic series, charged or neutral acids, etc.) in two solvents, k and s, one would expect a wide spectrum of the values of slope $b_i = b_s/b_k$ and

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within the reaction series of the acidic dissociation of neutral and cationic acids was discussed in Refs. 5-7.

intercept a_i which characterizes various reaction series and combinations of solvents. To our mind, the latter conclusion also emerges from the data in Table 2 and from a fan-like location of several separate straight lines in Fig. 1. Meanwhile, one can notice that the values of the intercepts a_1 for different reaction series vary rather significantly, from -2.7 (ortho-phenols) to +3.7 (secondary ammonium ions), which definitely is beyond any error limit assigned to the a_i values. Close values of a_i for some reaction series (see Table 2) are most probably exceptions not confirming the common trend.

In a future work a further study of some of the considered reaction series (e.g., 2-,3- and 4-substituted phenols) seems desirable. Alongside with the accumulation of additional data for these reaction series the inclusion of some other reaction series (e.g., dissociation of pyridinium ions, anilinium ions, etc.) into the analysis in terms of Eq. (1) also seems reasonable. A research into the acid-base equilibria in considerably more concentrated aqueous solutions of Bu_4NBr is also helpful for the modeling of the influence of the solvent-solute interactions on the acidity of neutral and cationic acids considered in the present work and in literature[11,12]. Work in these directions is in progress now.

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REACTIVITY OF DERIVATIVES OF PHENYLANTHRANILIC ACID. VII. ACID-BASE PROPERTIES OF DERIVATIVES OF PHENYLANTHRANILIC ACID IN BINARY SOLVENT DIOXAN-WATER

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Acid-base properties of biologically active derivatives of phenylanthranilic acid have been studied in binary solvent dioxan-water (60 volume % of dioxan) at 25° C. Influence of nature and position of substituents in a molecule on pK_a value was also analyzed. Correlation equations corresponding to the pK_a relationships to the Hammett σ-constants and to the σ_I and σ_C constants were calculated. It is shown that mostly the induction effect of a substituent affects the pK_a value. Transmission factor π' for fragment  -NH- was found (π' = 0.49).

Acid-base properties of 84 compounds were investigated at standard conditions in order to study the relationship between the chemical structure and biological effect of phenylanthranilic acid derivatives having various pharmacolo-

gically significant properties.

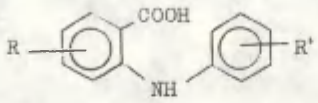
Ionization constants of the acids were determined by potentiometric titration in the binary dioxan-water solution (60 vol/% of dioxan) at 25° C. The experimental technique is described in the corresponding section.

It follows from Table 1 that the properties and position of substituents affects the value of ionization constants of the derivatives of phenylanthranilic acids in the anthranilic as well as in non-anthranilic fragments of the molecule. In both cases, the acceptor substituents lead to stronger acids, while the donor ones have the opposite effect. However, the sensitivity of the molecule to the introduction of the same substituent into the anthranilic and non-anthranilic fragments of the molecule is different: the introduction of the 4-NO_2 substituent into the non-anthranilic fragment reduces the pK_a value by only 0.58 units but in the anthranilic fragment, this substituent causes the pK_a drop by 1.35 pK_a units. This phenomenon may perhaps be explained by a rather long distance between the non-anthranilic fragment and the reaction center, as well as by the isolating effect of the -NH bridge group[2].

In the non-anthranilic fragment of the molecule, the substituent effect was quantitatively calculated by the Hammett equation (Table 2). The data in this table show that the values of constant ρ are quite close for all series studied (except nonsubstituted phenylanthranilic acids). The absolute value of constant ρ is small, i.e., the transfer of electronic effects of substituents to the reaction center via the NH bridge group is hindered ($\rho_{R\text{-}C_6H_4\text{-}COOH}$ = 1.47 in a 60 % aqueous dioxan[3]).

The use of induction constants of substituents (σ_I) in correlation constants $pK_a - f(\sigma_I)$ (Table 3) leads to a drastic deterioration of statistical characteristics. Consequently, in the case of the compounds studied, apart from the induction effect, the resonance effect of a substituent causes some additional influence onto the acid-base equilibria.

Ionization Constants pK_a of Derivatives of Phenylanthranilic Acids in Binary Solution of Dioxan and Water at 25°C



R' \ R	H	4-Cl	4-Cl,5-NO_2	3-NO_2	4-NO_2	5-NO_2	3,5-NO_2
1	2	3	4	5	6	7	8
H	6.65±0.04 6.96*	6.38±0.02 6.50*	5.08±0.04		5.30±0.07 5.42*	5.32±0.03 5.51*	4.06±0.01
2-CH_3	6.70±0.05 7.00*	6.46±0.04 6.65*	5.21±0.06	5.40±0.03	5.40±0.05 6.54*	5.44±0.04 5.60*	4.14±0.04 4.44*
3-CH_3				5.40±0.04			4.09±0.04 4.48*
4-CH_3	6.72±0.03 7.00*	6.48±0.04 6.62*	5.22±0.03	5.44±0.05	5.43±0.03 5.55*	5.54±0.04 5.63*	4.15±0.05 4.48*
2,4-CH_3			5.33±0.06				
3,4-CH_3		6.51±0.05	5.28±0.06	5.46±0.04			
2-OCH_3	6.82±0.04 7.12*	6.60±0.03 6.60*	5.30±0.05	5.50±0.04 5.79*	5.52±0.04 5.65*	6.51±0.06 5.69*	4.34±0.03 4.57*

Table 1 continued

1	2	3	4	5	6	7	8
3-OCH_3				5.24 ± 0.06		5.23 ± 0.02	
				5.59^{*}		5.48^{*}	
4-OCH_3	6.78 ± 0.04	6.59 ± 0.06	5.30 ± 0.03	5.48 ± 0.02	5.45 ± 0.04	5.50 ± 0.06	4.15 ± 0.04
	7.06^{*}	6.61^{*}		5.65^{*}	6.56^{*}	5.58^{*}	4.52^{*}
3,4-OCH_3					5.42 ± 0.05		
2-Cl	6.50 ± 0.07	6.25 ± 0.07	4.95 ± 0.06	5.14 ± 0.07	5.14 ± 0.06		3.90 ± 0.07
	6.82^{*}	6.31^{*}			5.38^{*}		
3-Cl		6.14 ± 0.06		5.00 ± 0.03		5.04 ± 0.05	3.74 ± 0.06
		6.26^{*}				5.30^{*}	
4-Cl	6.48 ± 0.05	6.30 ± 0.06	4.93 ± 0.06	5.15 ± 0.06	5.13 ± 0.05		3.90 ± 0.05
	6.84^{*}	6.29^{*}			5.25^{*}		
2-Br							3.90 ± 0.07
							4.35^{*}
3-Br		6.09 ± 0.05		5.00 ± 0.04			3.70 ± 0.03
							4.21^{*}
4-Br				5.14 ± 0.05		5.14 ± 0.05	3.93 ± 0.04
						5.29^{*}	4.26^{*}
3-I							3.80 ± 0.04
							4.27^{*}

Table 1 continued

1	2	3	4	5	6	7	8
4-I		6.08 ± 0.03 6.35^{*}					3.82 ± 0.03 4.26^{*}
3-NO_2		5.86 ± 0.06					
4-NO_2		5.80 ± 0.05					
Series	1	2	3	4	5	6	7

* The data of ref.[1] were obtained for the solutions of compounds with 0.01 M concentration.

Table 2

Parameters of Correlation Dependences $pK_a = pK_a^o + \rho\sigma$ of Derivatives of N-phenylanthranilic Acid

No Series	pK_a^o	ρ	n	S	r
1	6.63±0.02	-0.62±0.04	7	0.0019	0.992
2	6.38±0.03	-0.73±0.05	14	0.0044	0.987
3	5.09±0.01	-0.73±0.05	9	0.0012	0.997
4	5.30±0.01	-0.74±0.06	13	0.0022	0.993
5	5.30±0.02	-0.73±0.08	9	0.0020	0.991
6	5.33±0.03	-0.77±0.09	8	0.0038	0.982
7	4.04±0.03	-0.75±0.09	14	0.0042	0.970

$\bar{\rho}$ = 7.24

Table 3

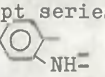
Parameters of Correlation Dependences $pK_a = pK_a^o + \rho_I\sigma_I$ of Derivatives of Phenylanthranilic Acid

No Series	pK_a^o	ρ	n	s	r
1	6.73±0.16	-0.35±0.27	7	0.1140	0.571
2	6.53±0.14	-0.85±0.31	14	0.1594	0.812
3	5.25±0.12	-0.47±0.35	9	0.3958	0.648
4	5.44±0.10	-0.69±0.32	13	0.1116	0.813
5	5.42±0.14	-0.41±0.39	9	0.1235	0.609
6	5.48±0.17	-0.66±0.43	8	0.1464	0.692
7	4.15±0.14	-0.63±0.32	14	0.1373	0.702

In order to estimate separately the effects of induction and of substituents' conjugation in the non-anthranilic fragment of the molecule, we have calculated the parameters of Eq. (1) given in Table 4:

$$pK_a = pK_a^{\circ} + \rho_I \sigma_I + \rho_C \sigma_C \qquad (1)$$

One should pay attention to the similarity of the ρ_I and ρ_C values, and to that of reaction constant ρ (Table 2), i.e., $\rho \approx \rho_I \approx \rho_C$. However, a comparison of the values of correlation coefficients r_{pK_a,σ_I} and r_{pK_a,σ_C} evidences a more substantial contribution of the induction effect in comparison with that of the conjugation (except series 1).

Transmission factor π' for fragment  was calculated by using the mean value of reaction constant $\bar{\rho}$ and $\rho_{R\text{-}C_6H_4COOH}$[3]

$$\pi' = \frac{\bar{\rho}}{\rho_{R\text{-}C_6H_4CHOH}} = 0.49 \qquad (2).$$

This value is in agreement with the transmission factor $\pi' = 0.44$ of the fragment -NH-  , which was calculated on the basis of the reaction of nucleophilic substitution of arylamines by picrylchlorides in benzene[4].

Experimental

Reagents. The dioxan used ("oscillating") was not purified additionally.

For preparation of mixed solutions, a freshly boiled bidistillate liberated from CO_2 was used.

The derivatives of phenylanthranilic acid were synthesized by a modified Ullman reaction[5-7]. The obtained compounds were recrystallized from ethanol three times and dried at 105° C up to the constant weight. The purity of the compounds was checked by thin-layer chromatography. The physi-

Table 4

Parameters of Correlation Dependence $pK_a = pK_a^{\circ} + \rho_I \sigma_I + \rho_C \sigma_C$ of Derivatives of Phenylanthranilic Acid

No Series	pK_a°	ρ_I	ρ_C	n	F	S	R	r_{pK_a,σ_I}	r_{pK_a,σ_C}
1	6.62±0.04	-0.60±0.16	-0.61±0.15	7	25.25	0.001	0.980	0.354	0.524
2	6.36±0.05	-0.68±0.08	-0.80±0.10	14	25.81	0.002	0.980	0.773	0.682
3	5.09±0.01	-0.74±0.03	-0.76±0.04	9	370.1	0.001	0.999	0.648	0.406
4	5.32±0.02	-0.76±0.06	-0.70±0.08	13	72.09	0.001	0.993	0.641	0.397
5	5.30±0.03	-0.73±0.08	-0.73±0.10	9	41.50	0.001	0.988	0.441	0.375
6	5.36±0.05	-0.84±0.11	-0.71±0.11	8	29.79	0.001	0.983	0.692	0.507
7	4.03±0.06	-0.73±0.15	-0.76±0.12	14	14.33	0.002	0.702	0.702	0.546

F - the Fischer criterion

R - multiple correlation coefficient

cochemical parameters of the substances obtained were in agreement with the data given in literature[5-7].

The methods of measurements were similar to those described in[8]. 0.05 M of aqueous solution of KOH purified from CO_2 served as a titrating agent. The concentration of the solutions titrated was 0.005 mol/l. Potentiometric titration was conducted on an ionometer EV-74, using a glass electrode ESP-43-074 and silver chloride electrodes EVL-1 M at 25° C. As a standard, the pK_a of acetic acid in the binary solvent of dioxan (60 vol/%)-water was determined (pK_a exp. = 7.50;5.52,7.49 [9]).

Three independent pK_a measurements were conducted for each compound. The accuracy of the results obtained was estimated by using the methods of mathematical statistics (at 0.95 reliability level)[10]. Calculations were performed on an "Elektronika-85" computer, using programs whose algorithms can be found in [11].

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C O N T E N T S